**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**
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# Non-variceal upper digestive bleeding: factors that influence evolution, with particular reference to the role of Helicobacter pylori

**PHD THESIS**
**Abstract**

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## CONTENT

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# INTRODUCTION

Upper gastrointestnal bleeding originates from the digestive segments located between the pharyngoesophageal junction and the duodenojejunal junction (delimited by Treitz's ligament). UGIB is revealed by haematemesis, melenemesis, melena or, in severe cases, by hematochesis.

In recent years there has been an increase in the incidence of upper gastrointestinal bleeding due to the increased consumption of anti-inflammatory drugs and the high prevalence (64%) of Helicobacter pylori infection. In the case of UGIB with H. pylori lesions as an etiology, accurate knowledge of the factors influencing evolution can significantly reduce the continuation of bleeding or the appearance of re-bleeding. In addition, most studies are focused on the involvement of H. pylori infection in the repair of those processes which have as a final point of evolution the neoplastic tansfomation, without assessing the impact of the bacterium in triggering acute hemorrhagic episodes of gastroduodenal H. pylori-positive lesions with hemorrhagic potential.

The main purpose of the paper is to analyze the factors that can cause an unfavorable evolution of non-variceal UGIB ( bleeding continuation or re-bleeding) due to lesion caused by H. pylori infection. Evaluating the factors that lead to an unfavorable prognosis for UGIB, regardless of etiology, the appreciation of relationships between alcohol consumption, non-steroidal anti-inflammatory drugs and antiplateletes drugs / anticoagulant drugs in these patients, developing an algorithm for an accurate diagnosis and for invasive and non-invasive surveillance and also estimating the costs of hospitalizing non-variceal UGIB H. Pylori positive patients represent secondary targets.

# CHAPTER I

## Acknowledgement stage

## Upper gastrointestinal bleeding. General data.

The frequency of UGIB is rather difficult to determine, but steadily increasing in recent years. It is estimated that the hospitalization rate for non-variceal digestive bleeding is 82.4 / 100.000. The incidence of UGIB is higher in patients over 60 years of age and mortality is present in about 8-14% of cases.

Positive diagnosis for upper digestive hemorrhage is established by anamnesis and objective clinical examination in about 90% of cases. At the same time, clinical and paraclinical examinations determine the existence and severity of bleeding. Paraclinical explorations are most frequently represented by laboratory analysis and superior digestive endoscopy. Currently, superior endoscopy definitely establishes the diagnosis of hemorrhage, appreciates the site, its severity, its situation (whether stopped or active), and in many cases may provide prognostic indications for the risk of re-bleeding.

The primary treatment for hemorrhage in ulcerous disease is endoscopic therapy in order to establish the cause of the bleeding, to estimate its severity and to reduce the risk of recurrent bleeding. The intensity of bleeding, its repetition, the cause which led to blood loss, the general condition of the patient at the time of hemorrhage onset, the promptness and the quality of treatment applied are factors on which the patient's survival depends. The main goal of the treatment is to stop the bleeding. This also accomplishes a number of secondary goals such as: reducing the blood demand for rebalancing, reducing the number of hospitalization days in the intensive care service, reducing the mortality. Re-bleeding occurs in 10-30% of endoscopically treated patients that is why a second endoscopic control is justified.

The surgical treatment of any hemorrhagic lesion that leads to superior digestive bleeding has a mortality up to 10 times higher if performed urgently, compared to the same intervention performed outside the hemorrhagic episode. The patient should be investigated endoscopically before any surgical intervention, with the purpose of diagnosing and localizing the hemorrhagic lesion. Treatment options for hemorrhagic ulcers include conservative interventions and gastric resection associated with gastric drainage procedures. Each specific surgical option is associated with its own incidence in the recurrence of ulcer, postgastrectomy syndrome and re-bleeding.

## CHAPTER II

## Helicobacter pylori infection. Generalities

About 20 years ago, Barry Marshall and Robin Warren described a bacteria in the human stomach, known as Helicobacter pylori. H pylori is a gram negative bacteria, measuring 2 to 4 μm length and 0.5 to 1 μm width. In developing countries, more than 80% of the population is H. pylori-positive, even young-aged people.

The prevalence of H. pylori in industrialized countries remains generally below 40%. H. pylori infection is a key factor in the etiology of various gastrointestinal diseases ranging

from chronic active gastritis without clinical symptoms to gastro-duodenal ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Gastric and duodenal ulcers are strongly related to the presence of H. pylori.

Diagnosis of H. pylori infection is determined by non-invasive and invasive tests. The invasive methods are: histological methods ("gold standard" in the diagnosis of H. pylori infection), cultures for H. pylori (the gold standard alternative) and rapid urease test (for qualitative detection of H. pylori). The non-invasive methods are: urea breath test (another alternative to the "gold standard"), antigen testing in faeces (sensitivity greater than 90%) and serology (with a sensitivtiy of 80-90%; it can’t prove the infection in progress due to immunological memory).

The eradication regimens for Helicobacter pylori include multiple treatment regimens with good results. At present, triple therapy based on proton pump inhibitors is the most commonly used scheme. This regimen includes the use of an PPI in combination with amoxicillin and clarithromycin. Treatment for H. pylori fails in approximately 20% of cases. Causes of therapeutic failure are antibiotic resistance and patient non-cooperation by giving up treatment.

## THE STAGE OF KNOWLEDGE

## Chapter III

## Material and method

Taking into account the progress made and mentioned in the problems due to non variceal UGIB that cause Helicobacter pylori lesions as an etiology, we intend to perform a retrospective study on a case of the last years (2014-2016). The study included a total of 283 patients who presented themselves to the Emergency Primary Unit with clinical signs of upper gastrointestinal haemorrhage and were admitted to the ATI Clinic, the Gastroenterology Clinic and the Surgery Clinic II of the County Emergency Clinical Hospital in Craiova, between the 1st of January 2014 and 31st of December 2016.

The diagnosis of patients with non variceal upper gastrointestinal haemorrhage was established both on the objective clinical examination and endoscopic exploration. The endoscopic examination was performed according to guidelines within the first 16-24 hours of admission. Hemodynamically unstable patients with specific signs of active upper

gastrointestinal haemorrhage, who remain unstable after following specific treatment, were subjected to emergency surgery for haemostasis.

Diagnosis of H. pylori infection was established by non-invasive methods (detection of specific antigen in faeces), histological (HE an Giemsa stains) and immunohistochemicals. Successful eradication of H. pylori infection was defined as negative results in antigen testing in faeces after specific therapy. The patient's evolution was analyzed in terms of the following parameters: in-hospital and remote mortality, re-bleeding rate, surgical and type of treatment, blood transfusion units, length of hospitalization. According to these ideas, the important part of the paper is structured in several chapters corresponding to two articles:

- Clinical endoscopic study of patients with non-variceal UGIB;
- Study of non-variceal H. pylori positive UGIB patients from an evolutionary, endoscopic, morphological and immunohistochemical (IHC) point of view.

In this study two types of endoscopic devices were used for endoscopic therapy and biopsy material harvesting: PENTAX EG-290 and EVIS EXERA III OLYMPUS. For data analysis, Microsoft Excel was used (Microsoft Corp., Redmond, WA, USA), together with XLSTAT 2014 add-on for MS Excel (Addinsoft SARL, PARIS, FRANCE) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA).

## CHAPTER V

### Results of the clinical and endoscopic non-variceal upper GI bleeding study

In the target group, during the 3 years of study, the frequency of UGIB is increased in male patients comparing to females, 198(76.15%) males and 62 (23.85%) females. Melena was present in 36.46% of the patients included in the target group. Association between hematemesis and melena was found in 24.62 % of the studied patients. Vomit with "coffee ground" aspect was found as first sign of upper G.I. bleeding in 10.77% of cases. Nota Benne – we considered the clinical signs found on the first consult in the emergency room, and, hematemesis was always accompanied by melena.

Patients with severe bleeding had a heart rate above 100 bpm, and in those cases with associated hypovolemic shock, an increase of this parameter was noticed, in contradiction with decreasing blood pressure. The heart rate was normal for a group of patients with hypovolemic shock, patients with chronic betablocant drugs which were administered 6 to 10 hours before the acute bleeding episode.

The AIMS 65 score, is a prognostic score used in assessing upper GI bleeding and can predict death, and the cost of hospitalization in these patients. This system consists of age, serum albumin levels, systolic blood pressure, INR and the presence/absence of consciousness. In this study we noticed a significant association between INR value and mortality, independently if the value that the other parameters included in the AIMS test have.

COX inhibiting anti-inflammatory drugs administered in the past 5 days were considered as risk factors. Four patients (32.31%) included in this study were administered these type of drugs for more than 5 days. Another 12 patients (4.62%) received non steroid anti-inflammatory drugs without medical guidance although they also received anti-platelet aggregation treatment for other cardiac conditions. We noticed that non steroid anti-inflammatory drugs are the main cause for bleeding from a peptic ulcer in young patients under 50 years of age.

From the 260 patients included in the study, (after excluding the lot of 27 patients diagnosed with bleeding peptic ulcer and also with esophageal varices), endoscopic exploration was performed for 212 patients (81.5%). This procedure was not performed for unstable patients and in those patients, conscious, which refused the procedure, 48 patients (18.46%).

The main causes of non variceal upper G.I. bleeding , diagnosed through endoscopy were: duodenal and gastric ulcer (chronic and acute) in 156 cases, haemorrhagic gastroduodenitis in 40 cases, postoperative peptic ulcer (anastomosis ulcer) in 4 cases, and other lesions in 12 cases (gastric cancer, polyps). Endoscopic hemostasis was performed in 96 cases (45.3%) for bleeding lesions classified in Forrest Ia, IIa and IIb. For patients with relapsed bleeding, another endoscopy was performed in 10 patients (4.7%), for lesions staged Forrest Ia, 3 patients with Ib, 2 with IIa, and 2 with IIb. From these patients, 5 needed emergency surgery for hemostasis. In 54,7% of patients with bleeding lesions staged IIc and III, endoscopic hemostatic procedures were used. In the case of these patients, we repeated the endoscopy due to bleeding relapse in 8 patients, from which 6 received endoscopic hemostasis, and 2 needed emergency surgery. From the 34 patients (13.08%) in which emergency surgery was performed, only 16 patients were investigated through endoscopy. The type of surgical protocol was established intraoperatively and we performed hemostasis on site, gastric resection with gastro-jejunal anastomosis or gastro-duodenal anastomosis, total

or subtotal gastrectomy, and cephalic or total pancreatoduodenectomy. Overeall mortality for operated patients was 23,5% (8 patients.)

Regarding blood transfusions, we noticed that for the patients with Upper G.I. Bleeding that were operated , the amount of blood transfusion needed was increased compared to the patients which received endoscopic hemostasis (3.94 units of blood versus 1.82 units.). Hospital stay for the patients had a mean of 5 days with minimum of 3 and maximum of 90 days. The patients which received an effective hemostasis technique stayed in the hospital between 3 and 5 days, those operated stayed in the hospital between 7 and 10 days, patietns with resections had a period of hospitalization between 10 and 12 days. The occurrence of complications (postoperative fistula) significantly prolonged the period of hospitalization.

## CHAPTER VI

### Results of batch analysis according to H. pylori

Testing for Helicobacter pylori was performed in 166 (63.85%) patients who presented themselves in the emergency room with non-variceal UGIB clinical signs without any previous history of haemorrhage. All patients enrolled in the study expressed their written consent for monitoring and treatment.

Fast diagnosis, hydro-electrolytic/volumic rebalancing and endoscopic or surgical haemostasis were primary steps in patient management with UGIB. Testing for Helicobacter pylori was performed after haemostasis. Non-invasive testing was performed by detecting H. pylori antigen, eliminated in the faeces by the immunochromatographic method. The test has an accuracy of over 90% for both diagnosis and confirmation of infection after treatment.

At the first non-invasive assessment (evaluation), immediately after the haemorrhagic episode, of the 166 patients tested for H. pylori in the faeces, 90 of them (54.21%) were positive and the remaining 76 patients (45.78%) were negative. At 30 days of discharge, all 166 patients were retested by the same method and the results were as follows:

- of the 76 initially negative patients, 70 (92.1%) remained negative, and 6 patients (7.9%) became positive (histological examination and IHC confirms their positivity for H. pylori).
- of the 90 initially positive patients who received specific treatment, 20 remained positive and 70 patients became negative.

Given the possibility of false-negative results in invasive testing, we decided that patients enrolled in the study should take endoscopy so as to histologically document the diagnosis of H. pylori infection. Endoscopic biopsy was obtained from the gastric mucosa from 5 different sites, according to the Updated Sidney System.

The results were as follows: 2 patients in the group of negative H. pylori subjects became positive by direct evidence of this bacterium. The two patients who were non-invasive were negative, and histology confirmed the presence of H. pylori received specific treatment. In another 4 patients IHC was needed for final diagnosis, so in two patients the diagnosis of intestinal metaplasia was established, to one gastric carcinoma was confirmed, and to the other one gastric lymphoma (MALT). Although the historical examination of H. pylori pathology is very loyal in providing data on atrophy, metaplasia or carcinoma, the addition of IHC examination adds more information and establishes the correct diagnosis in all cases. All patients received treatment with: omeprazole 20mg twice daily, amoxicillin 1g twice daily and clarithromycin 500 mg twice daily.

We found an increased frequency of haemorrhagic lesions among men in the group of H. pylori-positive patients compared to the group of men in the H. pylori-negative (80.04% vs. 70.83%). The presence of H. pylori increases in the studied group proportionally up to the age of 50, then slightly decreases in older ages. It should be noted that the prevalence of H. pylori infection is much higher among the population as compared to the study group, given that the diagnosis of H. pylori infection in these patients is established in a phase of haemorrhagic complications.

The main causes of haemorrhagic lesions in young patients (under 50 years of age) are H. pylori infection and NSAID use. After 50 years of age, NSAIDs replaced by the use of antiplatelet agents or oral anticoagulants. In the group of H. pylori positive patients, 56.5% of patients under the age of 50 stated that they had taken NSAIDs for more than 5 days, compared to only 16.6% of patients over 50 years old H. pylori-negative. Antiplatelet or oral anticoagulant therapies were direct causes of UGIB in 45% of patients with H. pylori positive gastro-duodenal lesions aged over 50 years.

Chronic alcohol consumption appears to have a similar effect to NSAIDs, so haemorrhage was considered to be determined in patients with H. pylori-positive lesions in approximately 14.29% of cases. In our study, 18.8% of H. pylori-positive patients, alcohol

users became negative after specific treatment, while 40% of all these patients remained positive after the specific therapy.

Aggressiveness and bacterial resistance to antibiotic therapy correlate positively with an increased rate of active bleeding. The assessment of patients with active bleeding during endoscopic examination revealed that the rate of bleeding was higher in H. pylori-positive patients who were negative after specific therapy (18.18%), than those with H. pylori negative lesions (15.79%) and much higher in patients resistant to treatment (40%). In most studies, haemorrhagic lesions were found to be unique in only 60% of cases of non-variceal UGIB; therefore, it is mandatory to highlight the entire upper digestive segment to confirm the single haemorrhagic lesion. These studies include in the evaluation of non-variceal upper gastrointestinal haemorrhage, haemorrhagic lesions independent of the presence of H. pylori.

Our study takes into consideration H. pylori positive patients and we found that the incidence of haemorrhagic lesions associated is much higher with H. pylori negative patients. Of the total H. pylori positive patients only 19.15% had associated gastrointestinal bleeding lesions compared with 33.33% of H. pylori-negative patients.

Approximately 16% of patients with non-variceal upper haemorrhage and H. pylori required surgery to stop bleeding. In the group of patients who were H. pylori-negative, the necessity of surgery was lower, respectively 9.7% of the patients underwent surgery (suture or resection). The need for haemostasis surgery is more common in patients with H. pylori-positive superior digestive haemorrhage. Regarding the type of surgery , in the case of H. pylori-positive patients, gastric resection was needed in several cases compared to the group of patients with H. pylori-negative haemorrhagic lesions. At the same time, postoperative complications occur more frequently in patients undergoing (gastrectomies, duodenopancreatectomies) than sutured patients. Thus, the presence of H. pylori contributes significantly to the increase in the duration of hospitalization and the treatment costs of these patients.

Distance mortality is influenced by the occurrence of bleeding, and in patients with non-variceal UGIB due to a H. pylori-positive lesion included in the study, this is lower compared to H. pylori-negative patients. We considered this difference due to the strict supervision of H. pylori-positive therapy and the patient’s information about his disease and its progression without treatment.

## CHAPTER VIII
## Conclusions

1. In the study group, the mean age of patients with nonvariceal upper gastrointestinal haemorrhage was 62.4 years. The highest incidence was achieved in the age group 60-79 years (46.12%) and there was an increased frequency of UGIH in males compared to women (76.15% vs. 23.85%). Increased incidence of nonvariceal upper gastrointestinal haemorrhage was associated with the consumption of NSAIDs, alcohol, oral anticoagulants, antiplatelets agents and high prevalence of H. pylori infection.

2. The proportion of nonvariceal UGIH patients who came from rural areas was higher than in urban areas (63.85% vs. 36.15%). Over 60% of rural patients over 25 years of age were diagnosed with UGIH at their first medical assessment, although the clinical symptom of peptic ulcer had begun a long time ago. The factors involved in recording these differences are related to poor medical education and poor accessibility to medical services.

3. The most frequent clinical manifestation of nonvariceal UGIH was melena (38.46%). Patients with haematemesis or coffee ground vomitus presented themselves earlier to their physician compared to patients with melena or hematochezia, and the association of haematemesis with hematochezia (4.62%) was a negative prognostic factor. All patients with this association of clinical signs required surgery.

4. Tachycardia was recorded in most patients with haemorrhagic shock. Although there are no studies that indicate the effect of beta-blockers on heart rate in patients with digestive haemorrhage, in our study, beta-blocking agents have significantly influenced heart rate. We believe that the Blatchford and Rockall prognostic score systems need to be adjusted considering this parameter.

5. UGIH diagnosis was established by anamnesis and clinical examination in most patients (95%), and upper digestive endoscopy confirmed the non-variceal origin. Endoscopic haemostasis was performed in 45.3% of patients.

6. The endoscopic techniques used to stop bleeding were: adrenaline injection, clip application, and electrocauterization. Re-bleeding has been correlated with the type of haemorrhagic lesion, and is more common with lesions classified as Forrest Ia and Ib. For 7% of patients whose endoscopic haemostasis failed, surgery was needed. Compared to surgical haemostasis, endoscopic haemostasis significantly reduced the requirement for transfusion

(1.86 units of whole blood versus 3.94 units of whole blood) and the duration of hospitalization (3 days vs. 10 days). Approximately 14% of patients, who had oral anticoagulant or outpatient antiaggregant agent, repeated the UGIH episode upon re-introducing oral medication, although haemostasis was performed.

7. Surgical treatment of nonvariceal UGIH was required in 34 patients (13.08%). The most common surgical complication when a resection technique was practiced was postoperative fistula, and the occurrence of this significantly prolonged the length of hospitalization.

8. In our study, overall mortality due to nonvariceal UGIH was 16.15%, and in operated patients it was 23.5%. Mortality correlated directly with age over 60 years, severe comorbidities, blood transfusion equal to or greater than 4 units, coagulopathies, haemoglobin and hematocrit values at admission.

9. In the studied group, of the 166 nonvariceal UGIH patients tested for H. pylori, 56.8% were positive and 43.2% were negative. Non-invasive testing by detection of H. pylori-specific antigen in feces has an increased sensitivity (90%) in the diagnosis and post-therapy evaluation of the infection. Although non-invasive testing has the advantage of availability and accessibility, histological and immunohistochemical methods are the most specific way of detecting this bacterium.

10. In patients with H. pylori-positive haemorrhagic lesions, the histological evaluation found associated lesions such as acute gastritis (31% of patients), atrophic gastritis (51%), intestinal metaplasia (14%) and gastric cancer (3 patients). The addition of IHC examination established the correct diagnosis in another 4 cases: intestinal metaplasia (2 cases), gastric carcinoma (1 case) and MALT (1 case). Routine IHC evaluation is limited due to the high cost and need for specialized personnel.

11. The prevalence of hemorrhagic lesions caused by H. pylori was increased in the young age segment (30-50 years), reaching another peak in the 70-79 age segment. Data from literature reports similar results.

12. We found an increased incidence of haemorrhagic lesions among H. pylori positive men compared to the group of men who were H. pylori negative (80.04% vs. 70.83%). H. pylori infection appears to be converging with other factors in favouring the onset of digestive haemorrhage.

13. The persistence of H. pylori infection in patients with previous gastric resections (4.1%) still predisposes to a haemorrhagic or neoplastic complication. In this context, additional investigations are needed to clarify the role of H. pylori in the recurrence of ulcers or gastric stump cancer.

14. In the under 50-year-old group, NSAID consumption and H. pylori infection had a cumulative effect in causing hemorrhagic lesions. After 50 years of age, NSAIDs were replaced with antiplatelet or oral anticoagulant therapies. In patients over 50 years of age who are recommended for this type of therapy, in addition to performing an upper digestive tract endoscopy, non-invasive testing for H. pylori is also required.

15. In our study, resistance to treatment was 22.2% (similar to other studies). All patients resistant to first line therapy were re-evaluated endoscopically and received second line therapy. The aggressiveness and resistance of H. pylori to antibiotic therapy correlates positively with an increased rate of active bleeding or re-bleeding.

16. Acute haemorrhagic lesions (acute gastric ulcer, acute duodenal ulcer, or haemorrhagic gastroduodenitis) were more commonly detected in H. pylori-positive patients versus H. pylori-negative patients (69 cases vs. 43 cases).

17. The need for surgically performed hemostasis was more frequent in patients with H. pylori-positive UGIH compared to H. pylori-negative (16% vs. 9.7%).

18. In patients with H. pylori positive haemorrhagic lesions, gastric resection was often required to produce hemostasis. Haemorrhagic H. pylori-positive lesions significantly contribute to increased hospitalization and treatment costs, and prophylaxis of re-bleeding and gastric cancer by eradicating this bacterium should become standard treatment in medical practice.

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