# STUDY PROTOCOL

# Outcomes of peptic ulcer bleeding in routine clinical practice

## Introduction

Acute upper non-variceal gastrointestinal bleeding is a very common cause of hospitalization worldwide, with an incidence that has been placed between 50 - 150 per 100,000 adults per year. Both gastric and duodenal ulcers are the most common cause of non-variceal upper-gastrointestinal bleeding. The mortality of peptic ulcer bleeding (PUB) has been reported to be between 5-14 % and remained stable despite the considerable advances observed in endoscopic and pharmacological treatments. The reasons for this are unclear, but a progressive aging population and the subsequent increase of co-morbidities may explain part of this apparent paradox.

Randomized clinical trials are the gold standard for determining the efficacy of therapies. Clinical guidelines and expert recommendations in the management of PUB are mostly based on these RCTs. The most recent RCT has reported that endoscopic therapy plus IV high-dose esomeprazole in high-risk patients for re-bleeding based on endoscopic findings, was associated with 5.9% of recurrent bleeding within 72 hours, 6.4% of endoscopic retreatment, 2.7% in need of surgery to control the bleeding event and a low mortality of 0.8% (Sung et al 2009). However, in agreement with regulatory agencies it is unclear or unknown how these recommendations are applied and the actual outcomes of PUB in clinical practice.

**Objectives:**

1. To assess outcomes in clinical practice in patients hospitalized due to PUB and treated with high-dose IV infusion PPI plus standard endoscopy therapy in patients with endoscopic high risk stigmata (spurting bleeding, visible vessel, oozing bleeding, red clot attached to the ulcer niche): overall and among individual PPI (esomeprazole and pantoprazole).

2. To assess outcomes in clinical practice in patients hospitalized due to PUB and treated with IV infusion PPI plus endoscopy therapy, if needed: overall and among individual PPI (esomeprazole and pantoprazole).

## Methods

## Study design and patients

This will be a multicenter retrospective observational study carried out in Spain. In order to prevent selection bias in pharmacotherapy, participating centers will be selected if they use routinely a single IV PPI (esomeprazole or pantoprazole) in the management of PUB events.

The eligible patients will be all consecutive patients hospitalized due to PUB and selected according to codes from ICD9 which identify gastric and duodenal ulcer bleeding (Table I). Patients will be included retrospectively from till completion of the desired sample size, which was estimated to be between ).

Eligible patients will be those complying with the following characteristics: a) age (≥18 years) admitted to the hospital with an overt upper GI bleed due to peptic ulcer and manifested as hematemesis/coffee ground vomiting, melena, hematochezia and other clinical or laboratory evidence of acute blood loss from the upper GI tract; b) evidence that an upper GI endoscopy was performed; c) IV PPI (esomeprazole or pantoprazole) had to be used after the endoscopy procedure d) complete medical records available for the study-related

hospitalization. Exclusion criteria are: patients with terminal malignant disease (life expectancy less than 6 months), required treatment with ASA or NSAIDs for the next 3 days during hospital after endoscopic therapy, or suffering from haematological disease associated with severe dyscrasia (e.g haemophilia)

Information regarding patient's characteristics, drug use before the PUB event, co-morbidities, symptoms, signs and severity of the event at hospital admission, endoscopic findings, endoscopic therapy, pharmacological therapy including type of drug, dose, route an type of administration, and outcomes will be collected from each patient's hospital medical records.

## Data, measurements and endpoint definitions

We will collect data recorded in charts in a pre-specified Case Report Form. Main data from each patient will include demographics, diagnostic procedures and both non-pharmacological and pharmacological treatments received by patients as summarized in Table II.

Therapeutic endoscopy will be considered any endoscopic action (injection, clips, thermo-coagulation, etc…) implemented to control the bleeding event in the presence of spurting bleeding, oozing bleeding, visible vessel, and/or clots attached to the ulcer niche. Endoscopic re-treatment will be considered when any repeated procedure occurred within 30 days from the index hospital admission due to re-bleeding from the PUB episode. High-dose IV PPI will be considered the administration of either esomeprazole or pantoprazole by infusion at the dose of 8 mg/hour. However, due to the variability of clinical practice and for the purpose of this study, the administration of equivalent doses of the PPI by injection within each 24-hour period will also be considered. The dose, route and type of administration will be recorded for each patient.

**Main outcomes:**

a) Bleeding continuation up to 3 days
b) Re-bleeding at 3, 7 and 30 days
c) Surgery at 3, 7 and 30 days
d) Mortality at 3, 7 and 30 days

***Definitions for outcome endpoints:***

a) Bleeding continuation up to 3 days after initial treatment:

1. Spurting from an artery at the initial endoscopic examination which did not respond to endoscopic therapy.
2. Persistence of bleeding following initial endoscopy determined by the presence of a red bloody naso-gastric aspirate, and/or shock with a pulse greater than 100 beats/min, a systolic blood pressure of under 100 mmHg, or both, and/or the need for substantial replacement of blood and fluid volume (transfusion of more than 3 units of blood within 4 h.) following endoscopic therapy and aimed to maintain the hemodynamic stability.

b) Re-bleeding at 3, 7 and 30 days is defined, following initial successful endoscopic treatment, including resuscitation if indicated, as recurrent vomiting of fresh blood, melena, or both with either shock or a decrease in haemoglobin concentration of at least 20 g/l This could occur during the same hospitalization and after discharge (up to 30 days from the PUB episode).

c) Surgery at 3, 7 and 30 days: the need of surgical intervention to control the bleeding event. This could occur during the same hospitalization and after discharge (up to 30 days from the PUB episode).

d) Mortality at 3, 7 and 30 days: Death of patients during hospitalization (in-hospital mortality) or after discharge (up to 30 days from the PUB episode).

1. Deaths will be related to the bleeding event: death from uncontrolled bleeding, death within 72 hours of endoscopy, death during surgery for uncontrolled bleeding, death from surgical complications or endoscopic-related death.
2. Deaths will be considered unrelated to the bleeding event if them were due to cardiac, cerebro-vascular, pulmonary or terminal malignant diseases or multi-organ failure causes.

e) Other outcomes will include days of hospitalizations, need of blood units transfused (total number).

Data management and quality assurance

A unique *Case Report Form* will be provided to all participating centers. There will be no possibility of adapting, changing or adding any different data to those gathered in the CRF. Although investigators from this hospital network in Spain have participated in a substantial number of studies collecting data either prospectively or retrospectively from charts, and in order to comply with data quality requirements, investigators will be trained in the use of CRF in advance (Lanas et al. Am J Gastroenterol 2009, ENERGIB study). Based on a sample of patients, investigators will also have to confirm in advance that medical records are compatible with the required data collection of the CRF. Furthermore, each CRF will be monitored for data consistency and accuracy. A sample of data recorded in the CRF from patients from each study centre will be evaluated by the study coordinator.

A specific computer program will be developed for data entry of each individual item collected in the CRF. Trained and experienced staff in managing databases will carry out the data entry. The database will be designed to minimize data entry errors,

In order to guarantee the confidentiality of the patients' data, only the hospital personnel will have access to the medical records. The study physicians will review the clinical charts and will fill in the data collection sheet with the relevant information. The clinical identification number will be recorded in the database

for data management purposes, but it will not be exported to the data analysis files to guarantee the patients' confidentiality. During the data entry process, a random fictitious identification number is created for each case, which will be the only identification available in the analysis files.

When the data collection and entry are completed, the information in the database will be exported to statistical analysis software, which will only contain the patients' fictitious identification created in the data entry process and not the clinical identification number, therefore preserving the patients' confidentiality during the data analysis process.

## Statistics

Sample size. Based on a recent international observational study on PUBs (Energib) the estimated re-bleeding rate was over 8% and the overall mortality rate of PUBs around 5%. It is assumed that these proportions will be increased between 1.5- and 2-fold in patients with high-risk stigmata that represent approximately between a third and a fourth of our total PUB study population. Assuming a 1.25% error for the lowest proportion and a 2.5% for the largest one, with an alpha value of 0.05, we have estimated a sample size of 1100 patients per group of PPI treatment for the overall PUB cohort to be studied and 400 - 500 per group (esomeprazole and pantoprazole) for those with high-risk stigmata.

Due to the study design, variables will be presented by descriptive statistics. Categorical data will be reported as frequencies and proportions. Continuous data will be reported as means and standard deviations. Where appropriate, alternate descriptive statistics such as quartile ranges, and medians with ranges for categorical and continuous data respectively will be reported. Analyses will be performed, overall, in patients with high-risk stigmata and according to individual PPI.

Although the objective of the study is to provide rates of outcomes of the different cohorts of PUB patients studied, potential differences in outcomes across different risk strata (age, co-morbidities, endoscopic findings, etc..) will be analysed with the Chi-square test for categorical variables and with t-test for continuous data. A variance analysis will be performed for multiple comparisons. Multivariable logistic regression models will also be fitted to define determinants of outcomes.

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**Table 1.** Description of CIE-9-MC Codes for gastrointestinal bleeding to be revised from to detect the population of the study

| Codes | Diagnosis | Source of the event |
|---|---|---|
| 531.xx (0.0 ;0.2 ;0.4 ;0.6 ;0.1 ;0 .5) | Gastric Ulcer | Upper GI |
| 532.xx (0.0 ;0.2 ;0.4 ;0.6 ;0.1 ;0 .5) | Duodenal Ulcer | Upper GI |
| 533.xx (0.0 ;0.2 ;0.4 ;0.6 ;0.1 ;0 .5) | Peptic Ulcer | Upper GI |
| 534.xx (0.0 ;0.2 ;0.4 ;0.6 ;0.1 ;0 .5) | Gastro-yeyunal ulcers | Probable Upper and Lower GI |
| 535.xx (.01) | Gastritis and duodenitis with bleeding | Upper GI |
| 578.x | Gastrointestinal Bleeding | Upper/Lower GI (validation process essential) |
| | | |

**TABLE 2: Variables to be collected (an appropriate CRF has been prepared ):**

**Patient characteristics**:

Sex and age.

Patient admitted from: own home, residential or nursing care, transferred from another acute hospital, other.

Date of hospitalization

Presence of symptoms at entry: red blood hematemesis, coffee ground vomits, melena, haematochezia, fresh red blood on rectal examination, shock,

Drug use before hospital admission: NSAIDs, ASA, PPI, among others

History/presence of co- morbidities and associated diseases: including CV, renal, liver, lung, diabetes, among others

**Management of PUB before endoscopy**

Hb/Hct at entry

BP and pulse

IV fluids

Units of Blood transfused

PPI: route, type of PPI, dose and type of administration

Vasoactive drugs: drug, route, dose and type of administration

Unit managing the PUB event

**Endoscopic Procedure**

Time from admission to endoscopy

Diagnosis:

Forrest classification

Presence of high risk stigmata: spurting, oozing, visible vessel, clot,

Therapeutic endoscopy: type

**Management of PUB after endoscopy**

PPI: route, type of PPI, dose, type of administration and time

Vasoactive drugs: drug, route, dose and type of administration

Units of blood transfused

H. pylori status, treatment

Unit managing the PUB event

**Outcomes Consistent with definitions**

Continuous bleeding

Rebleeding

Surgery to control bleeding

Other type of surgery

Need endoscopic treatment,

Need of 2nd endoscopic treatment

Death:

A.- Bleeding-related death
A1.- Died from uncontrolled bleeding.
A2.- Died within 72h of endoscopy.
A3.- Died during surgery for uncontrolled bleeding.
A4.- Died from surgical complications or within one month of surgery
A5.- Died from endoscopic-related mortality.
B.- Non- bleeding related death
B1.- Died of cardiac causes.
B2.- Died of pulmonary causes.
B3.- Died of cerebrovascular diseases.
B4.- Died of multi-organ failure (including liver and kidney failure).
B5.- Died of terminal malignant diseases.

Total number of units of blood transfused

Diagnostics test performed during hospitalization

Discharge date and admission date

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