Greek results of the "ENERGIB" European study on non-variceal upper gastrointestinal bleeding

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Abstract

Background Non-variceal upper gastro-intestinal bleeding (NVUGIB) is a common and challenging emergency situation. We aimed to describe the characteristics and clinical outcomes of patients with NVUGIB in Greece.

Methods ENERGIB (NCT00797641) was an epidemiological survey conducted in 7 European countries including Greece. It included adult patients with overt NVUGIB from 10 tertiary hospitals across Greece. Data for each patient were collected on admission and up to 30 days thereafter.

Results 201 patients were enrolled. A previous history of NVUGIB was reported by 14% of patients, while 61% had ≥ 1 co-morbidities. At presentation, 59% were on therapy that could harm the gastrointestinal mucosa, 14% on anticoagulant(s) and 42% had sign(s) of hemodynamic instability. 54% of patients showed stigmata of recent hemorrhage. Therapeutic endoscopy was performed in 25% and blood product(s) transfusions were required in 86% of cases. Proton pump inhibitors were administered before and after endoscopy in 70% and 95% of patients, respectively. Uncontrolled bleeding or rebleeding was observed in 11% being more common in elderly, hospitalized patients and patients with ≥1 co-morbidities. Second-look endoscopy was performed in 20%, angiographic intervention in 1.5% and surgical intervention in 4% of patients. Only 5/201 (2.5%) patients died during hospitalization and none died during the 30-day post-hospitalization period.

Conclusions The majority of patients with NVUGIB in tertiary Greek hospitals are elderly, with co-morbidities, hemodynamic instability and required transfusion(s), while one fourth undergoes therapeutic endoscopic interventions. However, NVUGIB is associated with moderate degrees of continued bleeding/re-bleeding, low surgical rates and, most importantly, low mortality.

Keywords gastrointestinal bleeding, endoscopy, co-morbidities, surgery, mortality

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Introduction

Non-variceal upper gastrointestinal (GI) bleeding (NVUGIB) is a universal common and severe cause of emergency hospital admission [1- 3]. Although the incidence of NVUGIB has decreased during the past few years [1,2], it is still an important cause of morbidity and mortality [3-9].

Despite decreased rates of re-bleeding [3,6,10,11], surgery [10], duration of hospitalization [11,12] and need for blood transfusions [11,12] by recent advances in both medical treatment and upper GI tract therapeutic endoscopy, the mortality from NVUGIB does not seem to have improved significantly [11-13]. The cause(s) remain unclear but seem to be related to advanced age and co-morbidities in patients with acute NVUGIB. However, early administration of potent anti-secretory agents and timely performed emergency therapeutic endoscopy may affect the outcome of acute NVUGIB. Thus, the detailed documentation of current clinical practices regarding treatment of acute NVUGIB could provide important information that may subsequently contribute to the development of protocols for the treatment of this emergency condition.

The aim of this study was to describe the clinical characteristics, the main diagnostic and therapeutic interventions, clinical outcome and potentially relevant prognostic factors in patients admitted for NVUGIB in Greek tertiary hospitals.

Materials and Methods

ENERGIB (ClinicalTrials.gov Identifier: NCT00797641; AstraZeneca study code: NIS-GEU-DUM-2008/2) was an epidemiological, retrospective study involving the participation of various hospital departments from 7 European countries (Belgium, Greece, Italy, Norway, Portugal, Spain, Turkey). This study included consecutive adult patients (aged ≥18 years) who were admitted for or developed NVUGIB during hospitalization in the participating sites. Patients were identified through discharge records. NVUGIB was diagnosed in patients presenting with hematemesis or coffee ground vomiting, melena, hematochezia, or any other clinical sign(s) or laboratory evidence of acute blood loss from the upper GI tract, confirmed by esophago-gastro-duodenoscopy. Patients with missing source documentation were excluded from the study. In the present study, only Greek hospital patients [10 major tertiary hospital departments in Athens (5), Thessaloniki (3), and Larissa (2)] were included.

The initial inclusion period was from October 1st to November 30th 2008. If the pre-defined number of patients was not enrolled during this period in any of the participating centers then the inclusion period was extended backwards in time until the appropriate target number of patients was reached. If the number of patients eligible for the study during the initial inclusion period was larger than that allocated for a particular site then the appropriate number of patients for this site was randomly selected and some patients were excluded from the study. The study complied with the Helsinki declarations and the final protocol was approved by the Scientific Committee of each participating site. Given the fact that the study was retrospective and non-interventional, the patients were treated based on the usual clinical practice of the participating sites.

Data were recorded retrospectively based on the patients' source documentation up to 30 days following an NVUGIB event. In particular, demographic details, diagnostic procedures, pharmaceutical and non-pharmaceutical therapeutic interventions as well as patients' clinical outcome were recorded.

Primary outcomes included continued bleeding following endoscopic hemostasis, re-bleeding, need for surgery to control bleeding (beyond endoscopy), in-hospital death and all-cause death during the 30-day post-NVUGIB period. The patients' outcomes after discharge were confirmed through telephone contacts in all cases. Continued bleeding was defined as arterial bleeding source during initial endoscopy not responding to endoscopic hemostasis or persisting after initial endoscopy, red blood content from nasogastric adsorption, tachycardia with pulses >100/min and/or systolic arterial pressure <100 mmHg, need for major blood transfusion (>3 blood units within 4 h) and/or volume expanders after endoscopy. Bleeding relapse was defined as a new hematemesis event with fresh blood and/or melena with shock or hemoglobin drop of ≥2 g/dL following initial successful treatment.

Statistical analysis

The analysis of the variables was performed using descriptive statistics. Qualitative data were presented as rates, and continuous data were presented as mean values and SD. Odds ratios (OR) and 95% confidence intervals (CI) were calculated based on logistic regression models. The statistical significance level was set at $P < 0.05$.

Results

The study enrolled 201 patients. Patient demographic and clinical data are shown in Table 1. The vast majority of patients (95%) were admitted as emergency NVUGIB cases and only 5% of them presented during hospitalization. Of the 201 patients, 69% were male, 14% had a history of at least one NVUGIB event in the past, 14% reported alcohol abuse, 22% were active smokers and 61% had at least one major co-morbidity. Additionally, more than 60% of the patients received non-steroidal inflammatory or antiplatelet potentially harmful drugs for the intestinal mucosa and 14% received anticoagulants. Only 10% of the patients received proton pump inhibitors (PPIs) before the bleeding event whereas a significant proportion also received other medication.

Eighty-four (42%) patients developed signs of hemodynamic instability defined as arterial systolic pressure <100 mmHg and/or heart rate >100/min, whereas 173 (86%) patients required blood transfusions. Endoscopy was performed within 36 h on average from admission and demonstrated endoscopic signs of recent and/or high-risk bleeding in 109 (54%) patients. Fifty (25%) patients required therapeutic endoscopic intervention. The majority of patients received PPIs before (70%) and

Table 1 Main acute non-variceal upper gastrointestinal bleeding patient characteristics

Number of patients	201
Mean age, years	66±15
Gender, men	139 (69%)
History of alcohol abuse	28 (14%)
Current smokers	44 (22%)
Patients with ≥1 major co-morbidity	123 (61%)
Medication	
Without medication	24 (12%)
Aspirin ≤100 mg/day	52 (26%)
Aspirin >100 mg/day	18 (9%)
Non-steroidal anti-inflammatory drugs	40 (20%)
COX-2 selective inflammatory drugs	4 (2%)
Selective platelet receptor inhibitors	12 (6%)
Coumarin anticoagulants	20 (10%)
Low-molecular weight coumarin	8 (4%)
Antidepressants (SSRI)	4 (2%)
Proton pump inhibitors	20 (10%)
Histamine type-2 receptor antagonists	2 (1%)
Other	72 (36%)
Acute NVUGIB history	28 (14%)
Hospital admission due to acute NVUGIB	
Emergency admission	191 (95%)
During hospitalization	10 (5%)

NVUGIB, non-variceal upper gastrointestinal bleeding

after (95%) endoscopy. Continued bleeding or re-bleeding was observed in 22 (11%) patients, whereas 40 (20%) were submitted to a second-look endoscopy (Table 2).

Angiography was performed in 3 (1.5%) patients, while 8 (4%) patients proceeded to surgery, 6 patients (3%) during hospitalization and another 2 (1%) patients during the 30-day post-hospitalization period. Five (2.5%) out of 201 patients died during hospitalization; none died within the 30 days following hospital discharge (Table 2). Out of the 5 deceased patients, 3 died due to uncontrolled bleeding and 2 due to cardiac cause.

Therapeutic endoscopy was performed far more frequently in men than in women (OR: 2.55, 95% CI: 1.14–5.70, P = 0.02) as well as in patients with duodenal ulcer (OR: 2.20, 95% CI: 1.13–4.28, P = 0.02). Continued bleeding was far less frequent in patients admitted as emergency NVUGIB cases compared with patients that developed NVUGIB during hospitalization (OR: 0.07, 95% CI: 0.02-0.28, P <0.001) and far more frequent in patients older compared to patients younger than 65 years (OR: 4.74, 95% CI: 1.12–20.09, P = 0.04) and in patients with than without at least one co-morbidity (OR: 5.03, 95% CI: 1.16-21.74, P = 0.03). Risk factors associated with re-bleeding

were similar (Table 3).

The possibility of surgery was related to the presence of at least one co-morbidity (OR: 5.72, 95% CI: 1.08–30.36, P=0.04), hematemesis (OR: 7.02, 95% CI: 1.61-30.61, P=0.01) and any risk score calculation for the severity of an NVUGIB event (OR: 7.69, 95% CI: 1.56-50.00, P=0.01). In contrast to the possibility of surgery, mortality was not related to any patient characteristics (Table 4).

Discussion

This epidemiological study showed that the majority of patients with NVUGIB in tertiary Greek hospitals were elderly, had at least one major co-morbidity, and received one or more concomitant medications that were potentially harmful to the GI mucosa. Only 14% of patients could recall a past NVUGIB event and 10% received PPIs prior to NVUGIB. Approximately 4 of 10 patients presented with signs of hemodynamic instability and more than 8 of 10 required blood transfusions. Emergency endoscopy was usually performed after the first 24 h from admission, but revealed endoscopic signs of recent and/or high-risk bleeding in more than 50% of patients, whereas therapeutic interventions were required in 1 of 4 patients. Notably, PPIs were administered to a high proportion (70%) of patients

Table 2 Severity, treatment and outcome of acute non-variceal upper gastrointestinal bleeding patients

Hemodynamic status	
No instability sign	117 (58%)
Tachycardia only	54 (27%)
Low blood pressure (Arterial pressure <100 mmHg)	23 (11.5%)
Low blood pressure (Arterial pressure <70 mmHg)	6 (3%)
Low blood pressure (Arterial pressure <50 mmHg)	1 (0.5%)
Use of proton pump inhibitors	
Before endoscopy	141 (70%)
After endoscopy	191 (95%)
Mean time from hospital admission until endoscopy, hours	36±140
Recent bleeding signs	109 (54%)
Therapeutic endoscopic intervention	50 (25%)
Blood transfusions, within 12 hours	173 (86%)
within 30 days	173 (86%)
Second-look endoscopy	40 (20%)
Continued bleeding/re-bleeding	22 (11%)
Angiography	3 (1.5%)
Surgery, during hospitalization	6 (3%)
during the 30-day post hospitalization period	2 (1%)
Death, during hospitalization	5 (2.5%)
during the 30-day post hospitalization period	0

Table 3 Factors possibly related to performing therapeutical endoscopy and acute non-variceal upper gastrointestinal bleeding continuation or re-bleeding

	Therapeutic endoscopy		Bleeding continuation		Rebleeding	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Gender (male : female)	2.55 (1.14 –5.70)	0.02	0.74 (0.26 – 2.06)	0.56	0.96 (0.34 – 2.74)	0.94
Age (>65 : ≥ 65 years' old)	1.07 (0.55 -2.07)	0.84	4.74 (1.12 – 20.09)	0.04	2.90 (0.85 – 9.90)	0.09
Co-morbidities (≥1 : none)	1.92 (0.97 -3.81)	0.07	5.03 (1.16 – 21.74)	0.03	3.14 (0.93 – 10.55)	0.07
Acute NVUGIB history (yes : no)	0.93 (0.36 -2.36)	0.87	1.38 (0.38 -5.07)	0.63	0.79 (0.18 – 3.41)	0.76
Admission (emergency : non-emergency)	0.57 (0.12 – 2.65)	0.47	0.07 (0.02 – 0.28)	<0.001	0.05 (0.01 – 0.21)	<0.001
Symptoms						
Hematemesis (yes : no)	1.45 (0.67 -3.12)	0.35	1.31 (0.41 – 4.13)	0.65	0.53 (0.12 – 2.28)	0.40
Melena (yes : no)	1.47 (0.53 -4.04)	0.46	3.19 (0.45 – 22.71)	0.25	3.07 (0.42 – 22.39)	0.27
Shock / cardiac arrest (yes : no)	0.80 (0.26 -2.45)	0.70	1.32 (0.29 – 6.11)	0.72	2.28 (0.59 – 8.80)	0.24
Coffee ground vomit (yes : no)	1.17 (0.46 -2.95)	0.75	0.74 (0.17 – 3.31)	0.70	0.76 (0.17 – 3.31)	0.72
Blood on a rhinogastric catheter (yes : no)	1.52 (0.16 -14.62)	0.72	-	-	-	-
Use of aspirin, NSAIDs or anticoagulants (yes : no)	1.76 (0.90 -3.43)	0.10	0.40 (0.14 – 1.15)	0.09	0.96 (0.36 – 2.58)	0.94
Risk score calculation (no : yes)	0.27 (0.10 -0.74)	0.01	0.86 (0.27 – 2.75)	0.80	0.63 (0.20 – 2.01)	0.44
Time to endoscopy (days)	1.00 (0.93 – 1.07)	0.98	0.98 (0.86 – 1.13)	0.83	0.72 (0.40 – 1.29)	0.27
Endoscopic diagnosis						
Esophagitis (yes : no)	0.42 (0.12 – 1.45)	0.17	1.18 (0.26 – 5.33)	0.83	0.49 (0.07 – 3.39)	0.47
Gastric ulcer (yes : no)	1.81 (0.92 – 3.53)	0.09	0.78 (0.25 – 2.48)	0.68	1.47 (0.54 – 4.02)	0.45
Duodenal ulcer (yes : no)	2.20 (1.13 – 4.28)	0.02	0.89 (0.30 – 2.61)	0.83	0.88 (0.31 – 2.53)	0.82

OR, odds ratio; CI, confidence interval; NVUGIB, non-variceal upper gastrointestinal bleeding; NSAIDs, non-steroidal anti-inflammatory drugs

immediately after their admission and before endoscopy, and in almost all (95%) patients after endoscopy. The characteristics of these patients were similar to those in NVGIB patients of previous studies conducted in Greece [14-17], and of the six European countries involved in the ENERGIB study, with the exception of the rate of co-morbidities that was lower (61%) for Greek and Turkish patients than that in other 5 European countries participating in this study (63-77%) (63%, 65%, 72%, 76% and 77%). Another interesting observation was the great variability in the use of PPIs before emergency endoscopy in the participating countries that ranged from as low as 33% in Belgium to 88% in Turkey [18].

Based on these data, the 30-day post-hospitalization mortality rate appeared to be relatively lower in this study of Greek patients (2.5%) than that reported in prior Greek and international trials [3,5,8,15-17,19,20]. Additionally, mortality in Greece was found to be the lowest among the 7 European countries participating in the ENERGIB study [18]. This relatively low mortality rate may be due to differences in patient characteristics, lower proportions of patients with in-hospital NVUGIB, differences or recent changes in NVUGIB treatment and/or systemic errors, such as reduced record of deaths within 30 days from NVUGIB initiation. The low proportion (5%) of our patients who developed NVUGIB during hospitalization might also have affected the low mortality rate. It should be noted that, in the ENERGIB study that recorded data using the same methodology in 7 European countries, the

basic characteristics of the Greek patients (Table 1) did not show any major deviations from those in patients from other participating European countries, except for the rate of at least one major co-morbidity, a known risk factor for increased mortality [3,6], which ranged from 61% to 77% in the participating countries in the ENERGIB study, as previously stated. In that study, the 30-day post-hospitalization mortality was also relatively low in Turkey (2.8%) and ranged between 3.5% and 8.0% in the other 5 countries [18].

Older studies have reported various prognostic factors for mortality in NVUGIB patients, including older age [3], presence and increased number of co-morbidities [3,6], continued bleeding and/or re-bleeding [6,14] and presence of red blood on a gastric aspiration catheter [6]. In the ENERGIB study, older age and presence of at least one co-morbidity were risk factors associated with death in NVUGIB patients [18]. However, this study was not adequately powered to detect risk factors for mortality in Greek NVUGIB patients especially because of the very small number of deaths (n=5). Thus, no conclusions about death risk factors can be drawn in our study.

Despite the relatively low mortality shown in our study, the characteristics of an NVUGIB event were not different in Greek patients than those reported in other countries. In particular, more than 10% of patients had continued bleeding or re-bleeding, whereas a second-look endoscopy was performed in 20%, angiography in 1.5% and surgery in 4% of the patients participating in our study. The rate of

Table 4 Factors possibly related to the need for surgery or mortality within 30 days after acute non-variceal upper gastrointestinal bleeding

	Surgery within 30 days		Mortality within 30 days	
	OR (95% CI)	P	OR (95% CI)	P
Gender (male : female)	0.38 (0.12 – 1.22)	0.11	0.29 (0.05 – 1.81)	0.19
Age (>65 : ≤65 years' old)	-	-	2.48 (0.27 – 22.61)	0.42
Co-morbidities (≥1 : none)	5.72 (1.08 – 30.36)	0.04	-	-
Acute NVUGIB history (yes : no)	-	-	1.50 (0.16 – 13.92)	0.72
Admission (emergency : non-emergency)	0.41 (0.05 – 3.16)	0.40	0.22 (0.02 – 2.11)	0.19
Symptoms				
Hematemesis (yes : no)	7.02 (1.61 – 30.61)	0.01	2.60 (0.42 – 16.09)	0.31
Melena (yes : no)	0.50 (0.12 – 2.12)	0.35	0.78 (0.08 – 7.21)	0.83
Shock / cardiac arrest (yes : no)	1.32 (0.18 – 9.39)	0.78	2.33 (0.25 – 21.92)	0.46
Coffee ground vomit (yes : no)	-	-	1.33 (0.14 – 12.31)	0.80
Blood on a rhinogastric catheter (yes : no)	-	-	-	-
Use of aspirin, NSAIDs or anticoagulants (yes : no)	0.41 (0.12 – 1.41)	0.16	-	-
Risk score calculation (no : yes)	0.13 (0.02 – 0.64)	0.01	1.68 (0.18 – 15.36)	0.65
Time to endoscopy (days)	0.93 (0.59 – 1.47)	0.75	0.46 (0.15 – 1.44)	0.19
Endoscopic diagnosis				
Esophagitis (yes : no)	-	-	-	-
Gastric ulcer (yes : no)	0.80 (0.19 – 3.44)	0.77	1.59 (0.26 – 9.74)	0.62
Duodenal ulcer (yes : no)	1.12 (0.30 – 4.21)	0.87	-	-

OR, odds ratio; CI, confidence nterval; NVUGIB, non-variceal upper gastrointestinal bleeding; NSAIDs, non-steroidal anti-inflammatory drugs

continued bleeding or re-bleeding was similar to that reported in prior studies [3,6,7,19]. Risk factors found to increase the possibility of continued bleeding or re-bleeding included the development of NVUGIB in hospitalized patients aged over 65 years with at least one co-morbidity. Major co-morbidity, endoscopic signs of high risk for bleeding, clinical severity at admission, bleeding duodenal ulcer, hematochezia, presence of red blood in a nasogastric catheter, smoking, non-use of PPIs after endoscopy and an inexperienced endoscopist have already been identified as additional risk factors for continued bleeding or re-bleeding in the literature [3,6,14,21]. In contrast, as it was documented in the ENERGIB study [16], older age, shock or cardiac arrest during hospital admission as well as a prior history of NVUGIB are additional risk factors for continued bleeding or re-bleeding.

This epidemiological study derived from current clinical practice in various tertiary hospitals in Greece provides new data regarding acute NVUGIB. Because this study recruited consecutive patients with an acute NVUGIB episode during a predefined enrollment period, we believe that these data truly represent patient characteristics and current practices in Greece. Limitations of this study were the retrospective design and involvement of multiple centers that may have allowed unidentified confounding factors to influence these results in a way that they should interpreted with relative caution. Additional limitations were the exclusion of patients due to missing data without further documentation and the

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Summary Box

What is already known:

- Non-variceal upper gastrointestinal bleeding (NVUGIB) is universally common and severe cause of emergency hospital admission
- The incidence of NVUGIB has decreased during the past few years, but it is still associated with increased morbidity and mortality
- Despite the improvements in both pharmaceutical treatment and endoscopic hemostatic techniques, mortality does not seem to have improved significantly

What the new findings are:

- The majority of NVUGIB patients currently hospitalized in tertiary Greek hospitals exhibit a considerable number of unfavorable risk factors, such as older age and major co-morbidities
- NVUGIB in Greece is associated with a relatively low continued bleeding and/or re-bleeding rate (11%)
- NVUGIB in Greece demonstrates low surgery rate and low mortality rate (<5%)

absence of report of the numbers of excluded cases. Thus, future properly designed prospective studies involving a large number of sites and patients are needed in order to confirm the findings of this study.

In conclusion, this study shows that the majority of NVUGIB patients currently hospitalized in tertiary Greek hospitals exhibit a considerable number of unfavorable risk factors, such as older age and major co-morbidities, and are frequently presented with hemodynamic instability and need for transfusions. NVUGIB in Greece is associated with a low probability for continued bleeding/re-bleeding (11%), which corresponds to the rates observed in other European countries, and also demonstrates low surgery and mortality rates (<5%).

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