Acute upper gastrointestinal bleeding in cirrhosis : Changes and advances over the past two decades

Jean Henrion, Pierre Deltenre, Stéphane De Maeght, Jean-Michel Ghilain, Jean-Marc Maisin, Michel Moulart, Thierry Delaunoit, Didier Verset, Ralph Yeung, Michael Schapira

Unité d'Hépato-Gastroentérologie, Hôpital de Jolimont, Haine-Saint-Paul, Belgium.

Abstract

Background and aims : **Few studies have compared two or more cohorts of cirrhotic patients admitted for upper gastrointestinal bleeding (UGIB) several decades apart. Our aim was to compare epidemiological, clinical, therapeutic and prognostic characteristics of UGIB (whatever the source) in two cohorts of cirrhotic patients admitted to the emergency room of the same general hospital 2 decades apart.**

Methods : **One-hundred cases of UGIB in cirrhotic patients consecutively admitted between 1984 and 1990 (cohort A) were compared with 100 similar cases admitted between 2004 and 2009 (cohort B).**

Results : **The sex ratio (M/F : 2/1), mean age (approximately 55Y) and the proportion of patients with alcoholic cirrhosis (approximately 80%) did not change. Mean Child-Pugh score and the proportion of patients in Child-Pugh stage C increased from 7.6 and 19% in cohort A to 8.8 and 35% in cohort B ($p < 0.001$). Therapeutic intervention was performed during initial endoscopy in 13 cases from cohort A and 50 from cohort B ($p < 0.001$), respectively. The number of transfused patients (85 in cohort A, 58 in cohort B) and the number of red blood cell units administered on the first day (median : 4 in cohort A, 2 in cohort B) were significantly decreased in cohort B ($p < 0.001$). The rate of rebleeding (45 in cohort A, 11 in cohort B), the need for rescue surgery (8 in cohort A, 0 in cohort B) and the in-hospital mortality (24 in cohort A, 9 in cohort B) significantly decreased in the more recent cohort ($p < 0.005$).**

Conclusion : **This study demonstrated that several characteristics of cirrhotic patients admitted with UGIB have changed over the past 2 decades. Above all, outcome has improved despite an increase in the severity of cirrhosis.** (Acta gastroenterol. belg., **2011**, 74, **381-388**).

Key words : cirrhosis, portal hypertension, upper gastrointestinal bleeding, variceal hemorrhage, outcome.

Introduction

Acute upper gastrointestinal bleeding (UGIB) in cirrhotic patients continues to have high rebleeding and mortality rates. Over the past two decades, new treatment modalities have been introduced and it is currently agreed that the outcome of UGIB in cirrhotic patients has improved especially when bleeding is of variceal origin. Mortality from variceal bleeding which was approximately 40% thirty years ago (1,2), is now estimated at around 20% at 6 weeks (3-9). Nevertheless, very few studies comparing 2 or more periods have been published (10-13) and those studies commonly suffered from one or more biases that were underlined by others (5).

The aim of the present study was to compare epidemiological, clinical, therapeutic and prognostic characteristics of UGIB – whatever the source of bleeding – in two cohorts of cirrhotic patients consecutively admitted to the emergency room of the same general hospital but at a two decade interval.

Patients and methods

This single-center study was conducted in a 600-bed general hospital. One-hundred cases of acute UGIB in cirrhotic patients consecutively admitted between 1984 and 1990 (cohort A) were compared with 100 similar cases admitted between 2004 and 2009 (cohort B). All patients admitted to the emergency room with UGIB (whatever the source) and cirrhosis were enrolled. Cases of UGIB occurring in patients already hospitalized were not included. The diagnosis of cirrhosis was confirmed by histology or was evident on clinical and imaging bases. UGIB was defined as hematemesis and/or melena and/or acute anemia associated with fresh blood at endoscopy. Bleeding relapse required 3 criteria : fresh hematemesis and/or melena, hemodynamic instability (blood pressure, pulse rate) and a drop in hemoglobin level. Selected demographic, clinical, biological, endoscopic, therapeutic and prognostic data were recorded on specially prepared files. The mortality rate was assessed as *in-hospital mortality*. The intake of potential gastro toxic drugs was recorded for the 5 days preceding the UGIB episode.

The collection of data was prospective in both cohorts. Patients from cohort A were selected from a large series of UGIB cases collected between April 1983 and April 1993. At this time, two of the authors of this study (J.H. and M.S.) were in charge of a medical intensive care unit (ICU) where all patients admitted to the hospital for UGIB were automatically transferred to. Pertinent data were prospectively collected. From this large series, we selected the 100 first cases of UGIB in cirrhotic patients, starting from January 1984. Patients

Correspondence to : Jean Henrion, Unité d'Hépato-Gastroentérologie, Hôpital de Jolimont, 159 rue Ferrer, 7100 Haine-Saint-Paul, Belgium.
E-mail : jeanhenrion@yahoo.fr

Submission date : 21/08/2010
Acceptance date : 15/03/2011

from cohort B were prospectively included from January 2004 in order to reach a cohort of 100 cases. Accordingly, this study compares 2 consecutive and prospectively collected cohorts of 100 cirrhotic patients admitted to the hospital for UGIB two decades apart.

Patient management

Cohort A – The first patient was enrolled on January 5, 1984 and the last patient on August 5, 1990. As already explained (see Patients and Methods), all patients were admitted to a medical ICU. Patients were treated using standard care procedures at the time. A central venous catheter was inserted for assessment and management of vascular filling. An arterial catheter was inserted in case of hemodynamic instability to monitor arterial pressure. Packed red blood cells were transfused to maintain Hb level at approximately 10 g/dl. The initial endoscopy was generally performed during the first 24 h after admission, mainly for diagnostic purposes. After the stay in the ICU, the patients were transferred to the hepato-gastroenterology unit. During this period, the mortality rate was not assessed at 6 weeks, as currently recommended following the Baveno Conference (14), but rather at the time of hospital discharge.

Cohort B – Patients in cohort B were enrolled between January 17, 2004 and June 22, 2009. The medical ICU not existing anymore, the hospital now houses a large intensive care department which includes 7 full-time ICU physicians. When a patient with cirrhosis and acute bleeding is admitted to the emergency room, he/she is put in charge of the emergency room physician and the on-duty senior gastroenterologist. Depending on the severity of bleeding and/or results of emergency endoscopy, the patient is transferred either to the intensive care department under the responsibility of the ICU physicians or to the hepato-gastroenterology unit. Current standard of care treatment is administered with somatostatine as the first-line vasoactive drug. Packed red blood cells are transfused if the Hb level is less than 8 g/dl. Current practice is to give antibiotics (norfloxacin or amoxicillin-clavulanic acid) to all cirrhotic patients. In case of admission to ICU, endoscopic control is generally performed prior to discharge and transfer to the hepato-gastroenterology unit in order to assess the risk of bleeding relapse.

Statistical analysis

Fischer's exact test and Mann-Whitney test were used to compare qualitative data and medians between the two cohorts.

Results

Demographic data, etiology and severity of cirrhosis and intake of gastrotoxic drugs are reported in table 1. The same proportion of a first episode of UGIB (approximately 55%) was observed in both cohorts. Gender and mean age did not change. The etiology of cirrhosis remained similar in both cohorts with alcohol (around 80%) as the main cause. The severity of cirrhosis according to the Child-Pugh score was significantly higher in cohort B. Over the past two decades, the mean Child-Pugh score increased from 7.6 to 8.8 ($p < 0.001$) and more patients were in stage C in cohort B ($p < 0.001$). The proportion of patients who took gastrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) at least once during the 5 days prior to the onset of UGIB was similar in both cohorts (approximately 25%), but motives for taking these drugs differed. In cohort B, significantly more patients took NSAIDs for analgesic use ($p < 0.001$) while ASA was generally consumed for cardiovascular reasons. In cohort A, ASA was still generally taken for analgesic or antipyretic use ($p < 0.001$).

Table 1. — **Epidemiological data in cohort A (1984-1990) and Cohort B (2004-2009)**

	Cohort A N = 100	Cohort B N = 100	*p*
Sex ratio (M/F)	64/36	66/34	*NS*
Mean age (range)	55 (22-85)	57 (30-82)	*NS*
Etiol. Cirrh. : Alc/Vir/Other	81/8/11	76/9/15	*NS*
1st UGIB episode	59	56	*NS*
Mean Child-Pugh score	7.67	8.82	*< 0.001*
Child-Pugh A/B/C	39/41/19(1)	14/51/35	*< 0.001*
Gastrotoxic Drugs	22/99	26/100	*NS*
NSAIDs	3	19	*< 0.001*
ASA (antalgic)	17	3	*< 0.001*
ASA (antiplatelet)	2	4	*NS*

Abbreviations : Alc : Alcohol ; ASA : Acetylsalicylic acid ; Etiol Cirrh : Etiology of cirrhosis ; NSAIDs : non steroidal anti-inflammatory drugs ; UGIB : upper gastrointestinal bleeding.
(1) : in cohort A, Child-Pugh score was calculated for 99 patients.

Table 2. — **Clinical and endoscopic data in cohort A (1984-1990) and cohort B (2004-2009)**

	Cohort A N = 100	Cohort B N = 100	*p*
UGIB manifestations			
Hematemesis	79	74	*NS*
Melaena	77	82	*NS*
Both	55	57	*NS*
Median Adm. delay (range)	8 h (1-240)	10 h (1-72)	*NS*
Median End. delay (range)	10 h (0-80)	3 h (0-60)	*< 0.001*
Hemodynamic data 1st day			
SAP < 100 mmHG	33	40	*NS*
Hb < 10 g/dl	78	84	*NS*
Hb < 8 g/dl	43	66	*0.001*
1st endoscopy observations	N = 97	N = 99	
Active haemorrhage	32	34	*NS*
Presence of blood	55	69	*0.06*
Presence of varices	83	90	*NS*

Abbreviations : Adm : admission ; End : Endoscopy ; Hb : hemoglobin ; SAP : systolic arterial pressure ; UGIB : upper gastrointestinal bleeding.

Table 3. — **Origins of upper gastrointestinal bleeding in cohort A (1984-1990) and cohort B (2004-2009)**

	Cohort A N = 100	Cohort B N = 100	*p*
Origins of UGIB *Var / Other / ENP*	65/32/3	55/44/1	*0.1*
Non-variceal origins	N = 32	N = 44	*0.1*
Peptic ulcer	12	17	
Gastric erosions	5	3	
Mallory Weiss	3	5	
PH Gastropathy	5	0	
Post treatment ulcer [(1)]	2	7	
esophagitis	0	5	
Other	3	5	
No lesion	2	2	

Abbreviations : ENP : endoscopy not performed ; PH : portal hypertensive ; UIGB : upper gastrointestinal bleeding ; Var : varices.
[(1)] : Post treatment ulcer : UGIB from esophageal ulcer related to variceal ligature.

Early clinical and endoscopic data are reported in table 2. The first manifestations of UGIB (hematemesis, melena) did not differ in the two cohorts. Median delay between the onset of UGIB and admission to the emergency room was similar, around 10 h. Hemodynamic parameters during the first 24 h following admission were not significantly different except for a lower level of hemoglobin in cohort B ($p = 0.001$). The median delay between admission to hospital and the first endoscopy was shortened from 10 to 3 h ($p < 0.001$). At endoscopy, active bleeding and/or presence of blood was similarly observed in both cohorts. Whether they were or were not the cause of bleeding, esophageal varices were present in the vast majority of patients. In 3 cases from cohort A and 1 case from cohort B, endoscopy was not performed because of cataclysmic hemorrhage and hopeless state of these moribund patients.

Sources of UGIB are reported in table 3. Variceal bleeding was the cause of 67% of UGIB episodes in cohort A and 55.5% in cohort B, but the difference was not significant ($p = 0.1$). The other main cause of bleeding was peptic ulcer. Bleeding from portal hypertensive gastropathy was reported in 5 cases in cohort A, but in none in cohort B. Conversely, esophagitis and post-treatment esophageal ulcers accounted for 12 cases in cohort B and only for 2 in cohort A.

Table 4. — **Therapeutic management in cohort A (1984-1990) and cohort B (2004-2009)**

	Cohort A N = 100	Cohort B N = 100	*p*
Endosc. Treat. 1st exam.	13/97	50/99	*< 0.001*
Sclerosing injections	13	37	*< 0.001*
Ligatures	0	20	*< 0.001*
other	0	3	*NS*
Drug treatment			
H_2RA	69	1	*< 0.001*
PPI	0	87	*< 0.001*
Somatostatine	53	81	*< 0.001*
Vasopressin	30	11	*< 0.001*
Balloon Tamponnade	29	4	*< 0.001*
Blood transfusions			
N transfused patients (total)	93	66	*< 0.001*
N transfused patients 1st day	85	58	*< 0.001*
N Units 1st day (med + range)	4 (1-43)	2 (1-10)	*< 0.001*

Abbreviations : Endosc. treat. 1st exam : endoscopic treatment performed during the initial endoscopy ; H_2RA : H_2-receptor antagonists ; PPI : proton pump inhibitors ; ICU : intensive care unit.

Table 5. — **Outcome in cohort A (1984-1990) and cohort B (2004-2009)**

	Cohort A N = 100	Cohort B N = 100	*p*
Bleeding relapse	45	11	*< 0.001*
Surgery	8	0	*< 0.001*
In-hospital mortality	24	9	*< 0.05*
Death delay *(days, med+range)*	10 (1-60)	6 (1-25)	*< 0.05*

Therapeutic management of these patients is summarized in table 4. As previously explained (see *Patients and Methods*), all patients in cohort A were automatically admitted to a medical ICU. For cohort B, 73 patients were admitted to the general intensive care department. A therapeutic intervention was more often performed during initial endoscopy in the more recent cohort ($p < 0.001$). Anti-acid drugs were commonly used in both cohorts even in case of variceal hemorrhage. In the 1980's, H_2-receptor antagonists were used, while proton pump inhibitors are currently used ($p < 0.001$). Vasoactive drugs were commonly administered during both periods, but recently somatostatine has most often been used as first-line treatment while vasopressin analogues were less frequently used ($p < 0.001$). Balloon tamponade was used in 29 cases during the 1980's, but in only 4 cases recently ($p < 0.001$). The proportion of patients transfused on the day of admission or during the course of their entire stay in the hospital has significantly decreased as has the number of packed red blood cell units given on the first day ($p < 0.001$, table 4).

The outcome of these cirrhotic patients admitted for acute UGIB is summarized in table 5. The rate of rebleeding, the need for rescue surgery and in-hospital mortality, all have significantly decreased ($p < 0.001$). Nevertheless, when outcome of UGIB of variceal origin was compared with non variceal origins, improvement was only observed for variceal hemorrhage ($p < 0.05$, table 6). It is noteworthy that the decrease in mortality was mainly observed in patients in Child-Pugh stage C (Table 6). In cohort A, 14/19 (74%) patients in Child-Pugh stage C died while mortality decreased to 6/35 (17%) in cohort B ($p < 0.001$). The mortality rate for patients in Child-Pugh stage A was nil in the more recent cohort.

Discussion

The aim of this study was to investigate changes in epidemiological, clinical, therapeutic and prognostic characteristics of cirrhotic patients urgently admitted to hospital with UGIB over the past two decades. This study has some limitations, but also some strength. The main limitation is that the data in cohort A is derived from a retrospective analysis of prospectively collected data and some pertinent data were not recorded in the

Table 6. — **Outcome according to the etiology of UGIB (variceal bleeding versus other causes) and the severity of cirrhosis (Child-Pugh Stages)**

	Cohort A[1] N = 97	Cohort B [1] n = 99	*p*
Variceal bleeding	65	55	*0.1*
Relapse	33 (50.7%)	8 (14.5%)	*< 0.001*
Death	20 (30.7%)	3 (5.5%)	*< 0.001*
Other sources of UGIB	32	44	
Relapse	11 (34.3%)	3 (6.8%)	*0.002*
Death	1 (3%)	5 (11%)	*NS*
Child Pugh A/B/C	39/41/19	14/51/35	*< 0.001*
Death CP-A	2/39 (5%)	0/14 (0%)	*NS*
Death CP-B	7/41 (17%)	3/51 (6%)	*0.08*
Death CP-C	14/19 (74%)	6/35 (17%)	*< 0.001*

Abbreviations : CP : Child-Pugh.
[1] – Four patients died before endoscopy could be performed, 3 in cohort A et 1 in Cohort B.
– The Child-Pugh score of one patient in Cohort A was not recorded.

1980's. For examples, prophylactic treatment with beta blockers for cirrhotic patients at risk of bleeding, prophylactic or therapeutic antibiotherapy, exhaustive assessment of co-morbidities and mortality rate at six weeks were not systematically recorded in cohort A. In contrast, this study has several strengths that are not found in similar studies comparing cohorts of cirrhotic patients admitted to hospital for UGIB at different periods (10-13). Its robustness is enhanced by the prospective collection of data, exhaustive inclusion of all admitted patients with cirrhosis and UGIB without any exclusion criteria, and enrollment at the same center under the care of the same medical team. Moreover, our center is a general hospital ; therefore, any "referral bias" which was pointed out by others (5) was also avoided. No patient was referred from another hospital. The table 7 summarizes the results of the few studies comparing UGIB in cirrhotic patients at different periods (10-13). It is also important to emphasize that the proportion of patients suffering from a first episode of UGIB was similar in both cohorts (59 in cohort A versus 56 in cohort B, table 1). In our opinion, this point is essential for the robustness of the study even though the outcome of a first episode of bleeding historically considered as more life-threatening (15) does not appear to differ from the outcome of relapse episodes in recent studies (3,6,10).

The main points that warrant comment concern epidemiological, therapeutic management and outcome of these cirrhotic patients admitted for acute bleeding two decades apart.

Epidemiological features

In contrast with many other reports, our study included not only variceal bleeding but also all other sources of UGIB. It is generally agreed that variceal bleeding accounts for approximately 70-80% of all UGIB in cirrhotic patients (4,16) and this figure was indeed observed in several recent studies (6,8,9,17-19). In our study, 67% (65/97) of UGIB were of variceal origin in cohort A and only 55.5% (55/99) in cohort B ($p = 0.1$). We have no explanation for this discrepancy, but other recent studies have reported similar figures (7,20).

During the past two decades, several epidemiological features of cirrhotic patients admitted for UGIB have remained stable. The sex ratio (M/F : 2/1) and mean age (around 55 years) have remained the same. This is in line with other studies comparing two separate periods (Table 7). The etiology of cirrhosis in case of UGIB (80% due to alcohol) has also remained the same (Table 1). It is interesting to point out that alcoholic etiology does account for less than 80% in our general population of patients with cirrhosis. In an observational study of 468 cirrhotic patients consecutively seen at the liver outpatient clinic between January 1995 and June 2001, 282 (60%) had alcoholic cirrhosis and 141 (30%) had viral cirrhosis (21). Thus, alcoholic cirrhosis would appear to be more subject to bleeding than cirrhosis due to other causes. This is in line with the observation that esophageal varices develop more rapidly when cirrhosis is of alcoholic origin (4). The incidence of variceal bleeding did not change. In cohort A, 65 patients experienced variceal bleeding during a 76-month period (incidence : 0.85/month) while the incidence in the more recent cohort B was 55 cases during a 66-month period (incidence : 0.83/month). This may appear surprising in view of the widely performed screening for esophageal varices and the recommended prophylactic treatment in case of large varices. However, this is in agreement with other studies showing no decrease in the prevalence of variceal hemorrhages (22-24). Despite the widely recognized efficacy of prophylactic treatment of cirrhotic patients with large varices, the overall incidence of variceal bleeding has not changed. There are several explanations for this. The burden of cirrhosis is growing

Table 7. — **Summary of the studies comparing two cohorts of cirrhotic patients admitted for upper gastrointestinal bleeding on two periods apart**

	El Serag 2000 (11)	Carbonell[1] 2004 (10)	Jamal 2008 (13)	Hobolth 2010 (12)	Henrion This study
Design	Retrospective Database VA	Retrospective Tertiary center	Retrospective National database	Retrospective Tertiary center	Prospective General hospital
Periods					
P1	1981-82	1980 and 1985	1988-90	1983-87	1984-90
P2	1988-91	2000	2003-04	2000-07	2004-09
N.patients					
P1	1339	114	121,092	56	100
P2	3636	83	*(1988-2004)*	111	100
Source of UGIB	Variceal	Variceal	Variceal	Variceal	All UGIB
Mean age (years)					
P1	55	56	55.4	54	55
P2	57*	56.3	*(Whole cohort)*	56	57
Child Pugh C					
P1	/	31.5%	/	/	19%
P2	/	45%	/	/	35%
Relapse	*30-day*	*In-hospital*		*5-day*	*In-hospital*
P1	30%	33.3%	/	35.7%	45%
P2	20%*	13,6%*	/	26.1%	11%*
Mortality	*6-week*	*In-hospital*	*In-hospital*	*6-week*	*In-Hospital*
P1	32%	35%	18%	30.4%	24%
P2	24%*	14.5%*	11.5%*	17.1%*	9%*

Abbreviations : P : period ; UGIB : upper gastrointestinal bleeding ; VA : department of the Veteran Affairs.
* : significant difference between both cohorts.
[1] : In the study of Carbonell, five 1-year periods were compared. The results of the first (1980) and the second (1986) are compared with the last (2000) in this table.

in many western countries due to an increase in the consumption of alcoholic beverages and progression of epidemics of chronic liver diseases linked to hepatitis C infection and non-alcoholic steatohepatitis. A more pertinent reason could be the increasing prevalence of advanced liver disease (Child-Pugh stage C) in the general cirrhotic population. In a French liver unit, the prevalence of cirrhotic patients with UGIB in Child-Pugh stage C increased from 21% in 1980 to 45% in 2000 (10). Similar results were reported in a study comparing two large cohorts of cirrhotic patients with variceal bleeding admitted 10 years apart (11) : in the 1981-82 cohort which included 1,339 patients, the prevalence of ascites and encephalopathy were 13.3% and 8.9%, respectively, in comparison with 24.6% and 13.6% in the 1988-91 cohort which included 3,636 patients (11). The increase in the severity of cirrhosis was also clearly apparent in our study (table 1) : The mean Child-Pugh score and the proportion of patients with Child-Pugh stage C were 7.6 and 19% in cohort A and 8.8 and 35% in cohort B, respectively ($P < 0,001$). In the large majority of recently published series of cirrhotic patients admitted with UGIB, the proportion of cases in Child-Pugh stage C was higher than 30% (3,5,6,9,10,17,18, 25,26). The increase in the severity of liver disease observed in cirrhotic patients admitted for UGIB is the result of improved survival of these patients.

The intake of gastrotoxic drugs is another epidemiological feature that has changed. In fact, the proportion of patients who took some NSAIDs or ASA (approximately 25%) did not differ between the two cohorts (Table 1). However, the doses and reasons for drug consumption changed (Table 1). In the 1980's, ASA was taken at high doses for its analgesic effect, while at present, ASA is more often taken at low doses due to its preventive vascular effect. The intake of NSAIDs was significantly higher in the more recent cohort (Table 1). Similar or even higher consumption of NSAIDs has been reported in recent studies (6,9,10) despite their well recognized harmful effects on gastric mucosa and their possible detrimental effect on the risk of variceal bleeding in cirrhotic patients (27,28). Increasing intake of NSAIDs could be another explanation for the absence of a decreasing incidence of variceal bleeding.

Therapeutic management

Therapeutic management of cirrhotic patients admitted for UGIB has progressed considerably over the past two decades. Currently, at our center, these patients are not automatically admitted to the ICU as they were in the 1980's. As already explained (see *Patients and methods*), the decision to transfer the patient to the ICU or to the hepato-gastroenterology unit is shared between the emergency room physician and the senior gastroenterologist on duty. Initial endoscopy is performed in the emergency ward, in the ICU or most often in the endoscopy room. The median time elapsing between admission of the patient and initial endoscopy was shortened from 10 h in the 1980's to 3 h in the 2000's ($p < 0.001$, table 2). The shortening of this delay is not the result of a concerted decision based on widely recommended guidelines. Rather, it can be explained by the desire of the intensive care physicians to have endoscopy performed as soon as possible and by our expanded gastroenterology team. In the 1980's, there were only 2 full-time gastroenterologists. We now number 8. Thus, the endoscopy room at our center functions all day from morning to evening.

A major change in therapeutic management of UGIB in cirrhotic patients lies in therapeutic intervention during initial endoscopy. Endoscopic treatment at the time of the first endoscopy was performed in half of the patient in cohort B and in only 13% in cohort A ($p < 0.001$, table 4). In the early 1980's, endoscopic treatment was at its beginning and often was not performed during the first urgent endoscopy, but rather during another elective examination (10,11,22). The use of Balloon tamponade has virtually disappeared (29 cases in cohort A versus 4 cases in cohort B, $p < 0.001$) and was recently used only in the case of cataclysmic life-threatening hemorrhage as it is at present recommended (14,16) and widely applied in recent series (5,6,10,29,30). It is interesting to note that hepato-gastroenterologists and ICU physicians continue to inhibit gastric acid secretion even in case of variceal hemorrhage. Drugs inhibiting gastric acid secretion were used in more than 90% of patients in both cohorts. In the 1980's, H_2-receptor antagonists were used, while proton pump inhibitors are used today. Some authors have underlined that anti-acid drugs were often used in cirrhotic patients without evidence based practice (31). In addition to early endoscopic treatment, another major change in the management of these patients lies in the decrease of blood transfusions. In the 1980's, the goal was to maintain the hemoglobin level at approximately 10 g/dl ; currently, it is recommended that hemoglobin level being maintained between 7-8 g/dl (4,14,32). Studies on animal models of cirrhosis have shown that portal pressure tended to rapidly increase in case of transfusion, even in the absence of over-transfusion (33). Moreover, blood transfusion has an immunosuppressive effect leading to increased infection rates (34-36). A recent randomized study, published as an abstract, showed that in cirrhotic patients admitted for UGIB, the risk of rebleeding was higher in the case of "classical" transfusion than that of restricted transfusion (37). Accordingly, the proportion of transfused patients and the number of transfused packed red blood cell units have significantly decreased in cohort B (Table 4).

Outcome

Recent studies have shown that the outcome of cirrhotic patients admitted with UGIB has improved over past decades if we compare mortality and rebleeding rates with previous historical studies (38). To our knowledge, only 4 studies comparing two or more separate periods have been published (10-13) and all 4 suffered from one or more biases. These biases include retrospective analysis of data, multicenter enrollment of patients, use of selection criteria and inclusion of patients referred to tertiary centers. Improvement in the prognosis of these patients could only be demonstrated in a study comparing cohorts of patients recruited under similar conditions and admitted to the same non-tertiary center (5). Our study met these conditions and confirmed that the outcome of cirrhotic patients with acute UGIB has improved over the past two decades (Table 5). The rate of rebleeding, the need for surgery and the mortality rate, all have significantly decreased despite the increase in the severity of cirrhosis. This is the main result of the present study and this result is in line with the 4 comparable studies showing a decrease in mortality and rebleeding rates despite higher degree of cirrhosis severity (11,12). The mortality rate in our patients with Child-Pugh stage A cirrhosis was nil like in recent studies (7,11,28) and the mortality rate of patients with Child-Pugh stage C has largely improved (Table 6). Improvement in the outcome of these patients may be attributed to advances in the supportive care of patients in ICU (39). In our opinion, this is not the main reason. In the 1980's, our patients were already admitted to a specialized ICU and were managed according to standardized protocols under the care of competent medical and nursing staffs. Improvement in their outcome might be better explained by advances in therapeutic measures such as therapeutic endoscopy, appropriate use of vasoactive drugs (somatostatine and vasopressin analogues), restriction in the volume of transfusion and prophylactic use of antibiotics (19,40-42). However, in our study, improvement in the mortality rate of cirrhotic patients with acute UGIB was observed only in the case of variceal bleeding and not in the case of bleeding from any other cause (Table 6). This is in line with the literature showing improvement in the outcome of UGIB when the source of bleeding was of variceal origin, but not in the case of peptic ulcer (23,24,43).

In conclusion, the characteristics of UGIB in patients with cirrhosis have profoundly changed over the past 2 decades. Some epidemiological features, such as the

sex ratio, mean age and etiology of cirrhosis remain exactly the same. In contrast, the increase in the severity of cirrhosis is substantial. Yet despite the more severe stage of cirrhosis, all essential markers of outcome (rate of rebleeding, need for rescue surgery and mortality rate) have improved. Improvement in outcome could be explained by advances in therapeutic management of these patients.

References

1. GRAHAM D.Y., SMITH J.L. The course of patients after variceal hemorrhage. *Gastroenterology*, 1981, **80** : 800-809.
2. PINTO H.C., ABRANTES A., ESTEVES A.V., ALMEIDA H., CORREIA J.P. Long-term prognosis of patients with cirrhosis of the liver and upper gastrointestinal bleeding. *Am. J. Gastroenterol*., 1989, **84** : 1239-1243.
3. AUGUSTIN S., MUNTANER L., ALTAMIRANO J.T., GONZALEZ A., SAPERAS E., DOT J. *et al*. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. *Clin. Gastroenterol. Hepatol*., 2009, **7** : 1347-1354.
4. BOSCH J., BERZIGOTTI A., GARCIA-PAGAN J.C., ABRALDES J.G. The management of portal hypertension : rational basis, available treatments and future options. *J. Hepatol*., 2008, **48** Suppl 1 : S68-92.
5. CHALASANI N., KAHI C., FRANCOIS F., PINTO A., MARATHE A., BINI E.J. *et al*. Improved patient survival after acute variceal bleeding : a multicenter, cohort study. *Am. J. Gastroenterol*., 2003, **98** : 653-659.
6. D'AMICO G., DE FRANCHIS R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology*, 2003, **38** : 599-612.
7. DEL OLMO J.A., PENA A., SERRA M.A., WASSEL A.H., BENAGES A., RODRIGO J.M. Predictors of morbidity and mortality after the first episode of upper gastrointestinal bleeding in liver cirrhosis. *J. Hepatol*., 2000, **32** : 19-24.
8. SEO Y.S., KIM Y.H., AHN S.H., YU S.K., BAIK S.K., CHOI S.K. *et al*. Clinical features and treatment outcomes of upper gastrointestinal bleeding in patients with cirrhosis. *J. Korean Med. Sci*., 2008, **23** : 635-643.
9. THOMOPOULOS K., THEOCHARIS G., MIMIDIS K., LAMPROPOULOU-KARATZA C., ALEXANDRIDIS E., NIKOLOPOULOU V. Improved survival of patients presenting with acute variceal bleeding. Prognostic indicators of short- and long-term mortality. *Dig. Liver Dis*., 2006, **38** : 899-904.
10. CARBONELL N., PAUWELS A., SERFATY L., FOURDAN O., LEVY V.G., POUPON R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology*, 2004, **40** : 652-659.
11. EL-SERAG H.B., EVERHART J.E. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. *Am. J. Gastroenterol*., 2000, **95** : 3566-3573.
12. HOBOLTH L., KRAG A., BENDTSEN F. The recent reduction in mortality from bleeding oesophageal varices is primarily observed from Days 1 to 5. *Liver Int*., 2009.
13. JAMAL M.M., SAMARASENA J.B., HASHEMZADEH M. Decreasing in-hospital mortality for oesophageal variceal hemorrhage in the USA. *Eur. J. Gastroenterol. Hepatol*., 2008, **20** : 947-955.
14. DE FRANCHIS R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J. Hepatol*., 2005, **43** : 167-176.
15. CHRISTENSEN E., FAUERHOLDT L., SCHLICHTING P., JUHL E., POULSEN H., TYGSTRUP N. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. *Gastroenterology*, 1981, **81** : 944-952.
16. SHARARA A.I., ROCKEY D.C. Gastroesophageal variceal hemorrhage. *N. Engl. J. Med*., 2001, **345** : 669-681.
17. ABID S., JAFRI W., HAMID S., SALIH M., AZAM Z., MUMTAZ K. *et al*. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation : a randomized double-blind placebo-controlled trial. *Am. J. Gastroenterol*., 2009, **104** : 617-623.
18. CARDENAS A., GINES P., URIZ J., BESSA X., SALMERON J.M., MAS A. *et al*. Renal failure after upper gastrointestinal bleeding in cirrhosis : incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology*, 2001, **34** : 671-676.
19. VIVAS S., RODRIGUEZ M., PALACIO M.A., LINARES A., ALONSO J.L., RODRIGO L. Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding. *Dig. Dis. Sci*., 2001, **46** : 2752-2757.
20. HSU Y.C., CHUNG C.S., TSENG C.H., LIN T.L., LIOU J.M., WU M.S. *et al*. Delayed endoscopy as a risk factor for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage. *J. Gastroenterol. Hepatol*., 2009, **24** : 1294-1299.
21. HENRION J., DE MAEGHT S., DELTENRE P., GHILAIN J.M., MAISIN J.M., SCHAPIRA M. *et al*. Impact of hepatitis C virus infection on the aetiology of cirrhosis and hepatocarcinoma in three affiliated hospitals in southern Belgium. *Acta Gastroenterol. Belg*., 2002, **65** : 80-82.
22. STOKKELAND K., BRANDT L., EKBOM A., HULTCRANTZ R. Improved prognosis for patients hospitalized with esophageal varices in Sweden 1969-2002. *Hepatology*, 2006, **43** : 500-505.
23. THOMOPOULOS K.C., VAGENAS K.A., VAGIANOS C.E., MARGARITIS V.G., BLIKAS A.P., KATSAKOULIS E.C. *et al*. Changes in aetiology and clinical outcome of acute upper gastrointestinal bleeding during the last 15 years. *Eur. J. Gastroenterol. Hepatol*., 2004, **16** : 177-182.
24. VAN LEERDAM M.E., VREEBURG E.M., RAUWS E.A., GERAEDTS A.A., TIJSSEN J.G., REITSMA J.B. *et al*. Acute upper GI bleeding : did anything change ? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am. J. Gastroenterol*., 2003, **98** : 1494-1499.
25. NIDEGGER D., RAGOT S., BERTHELEMY P., MASLIAH C., PILETTE C., MARTIN T. *et al*. Cirrhosis and bleeding : the need for very early management. *J. Hepatol*., 2003, **39** : 509-514.
26. SANDERS D.S., CARTER M.J., GOODCHAP R.J., CROSS S.S., GLEESON D.C., LOBO A.J. Prospective validation of the Rockall risk scoring system for upper GI hemorrhage in subgroups of patients with varices and peptic ulcers. *Am. J. Gastroenterol*., 2002, **97** : 630-635.
27. DE LEDINGHEN V., HERESBACH D., FOURDAN O., BERNARD P., LIEBAERT-BORIES M.P., NOUSBAUM J.B. *et al*. Anti-inflammatory drugs and variceal bleeding : a case-control study. *Gut*, 1999, **44** : 270-273.
28. YOSHIDA H., MAMADA Y., TANIAI N., MINETA S., KAWANO Y., MIZUGUCHI Y. *et al*. Interactions between anti-ulcer drugs and non-steroidal anti-inflammatory drugs in cirrhotic patients with bleeding esophagogastric varices. *Hepatogastroenterology*, 2009, **56** : 1366-1370.
29. ANANTHAKRISHNAN A.N., MC GINLEY E.L., SAEIAN K. Higher hospital volume predicts endoscopy but not the in-hospital mortality rate in patients with acute variceal hemorrhage. *Gastrointest. Endosc*., 2009, **69** : 221-229.
30. LO G.H., CHEN W.C., CHEN M.H., TSAI W.L., CHAN H.H., CHENG L.C. *et al*. The characteristics and the prognosis for patients presenting with actively bleeding esophageal varices at endoscopy. *Gastrointest. Endosc*., 2004, **60** : 714-720.
31. LODATO F., AZZAROLI F., DI GIROLAMO M., FELETTI V., CECINATO P., LISOTTI A. *et al*. Proton pump inhibitors in cirrhosis : tradition or evidence based practice ? *World J. Gastroenterol*., 2008, **14** : 2980-2985.
32. GARCIA-TSAO G., SANYAL A.J., GRACE N.D., CAREY W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*, 2007, **46** : 922-938.
33. CASTANEDA B., DEBERNARDI-VENON W., BANDI J.C., ANDREU V., PEREZ-DEL-PULGAR S., MOITINHO E. *et al*. The role of portal pressure in the severity of bleeding in portal hypertensive rats. *Hepatology*, 2000, **31** : 581-586.
34. BARKUN A.N., BARDOU M., KUIPERS E.J., SUNG J., HUNT R.H., MARTEL M. *et al*. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann. Intern. Med*., 2010, **152** : 101-113.
35. DUGGAN J.M. Gastrointestinal hemorrhage : should we transfuse less ? *Dig. Dis. Sci*., 2009, **54** : 1662-1666.
36. MOORE F.A., MC KINLEY B.A., MOORE E.E. The next generation in shock resuscitation. *Lancet*, 2004, **363** : 1988-1996.
37. COLOMO A., HERNANDEZ-GEA V., MUNIZ-DIAZ E., MADOZ P., ARACIL C., ALVAREZ-URTUTI C. *et al*. Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding. *Hepatology*, 2008, **48** : 413A.
38. MC CORMICK P.A., O'KEEFE C. Improving prognosis following a first variceal haemorrhage over four decades. *Gut*, 2001, **49** : 682-685.
39. CHOLONGITAS E., CALVARUSO V., SENZOLO M., PATCH D., SHAW S., O'BEIRNE J. *et al*. RIFLE classification as predictive factor of mortality in patients with cirrhosis admitted to intensive care unit. *J. Gastroenterol. Hepatol*., 2009, **24** : 1639-1647.
40. GARCIA-TSAO G., BOSCH J. Management of varices and variceal hemorrhage in cirrhosis. *N. Engl. J. Med*., 2010, **362** : 823-832.
41. JALAN R., HAYES P.C. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology. *Gut*, 2000, **46** Suppl 3-4 : III1-III15.
42. TANDON P., GARCIA-TSAO G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin. Liver Dis*., 2008, **28** : 26-42.
43. AABAKKEN L. Nonvariceal upper gastrointestinal bleeding. *Endoscopy*, 2005, **37** : 195-200.