Management practices for gastrointestinal hemorrhage related to portal hypertention in cirrhotic patients: evaluation of the impact of the Paris consensus workshop

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for the French national working group on portal hypertension

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SUMMARY

Objectives — The purpose of this before-after observational survey was to evaluate compliance with good clinical practice guidelines for gastrointestinal hemorrhage related to portal hypertension and the impact of the French Consensus Workshop held in Paris in 2003.

Methods — Data were recorded concerning episodes of gastrointestinal hemorrhage occurring in cirrhotic patients using a survey questionnaire in 2003 before the workshop and again in 2004.

Results — Seventy-six index episodes were included in 2003 and 84 in 2004 in patients attending French hospitals. Before hospital admission, primary prophylaxis was similar in 2003 and 2004, but β-blockers were used alone more often in 2004 for secondary prophylaxis (42% vs 19%, P=0.018). The time from onset of bleeding to hospital admission was greater than 12 hours for 43 and 42% of patients and was not shorter in the event of recurrent hemorrhage. At admission, vasoactive drugs were given earlier in 2004 (<2h: 68% vs 35%, P<0.001). Use of antibiotic prophylaxis was similar in 2003 and 2004 (70% vs 61%, P=0.098), and was more common for Child-Pugh B or C patients (P=0.044).

Conclusion — The Paris Consensus Workshop enabled improved clinical practices. Weak points were insufficient screening for cirrhosis, long delay before admission, insufficient use of antibiotic prophylaxis which should be systematic.

RÉSUMÉ

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Résultats — Soixante-six index episodes were included in 2003 and 84 in 2004 in patients attending French hospitals. Before hospital admission, primary prophylaxis was similar in 2003 and 2004, but β-blockers were used alone more often in 2004 for secondary prophylaxis (42% vs 19%, P=0.018). The time from onset of bleeding to hospital admission was greater than 12 hours for 43 and 42% of patients and was not shorter in the event of recurrent hemorrhage. At admission, vasoactive drugs were given earlier in 2004 (<2h: 68% vs 35%, P<0.001). Use of antibiotic prophylaxis was similar in 2003 and 2004 (70% vs 61%, P=0.098), and was more common for Child-Pugh B or C patients (P=0.044).

Conclusion — La Conférence de consensus de Paris a permis d’améliorer les pratiques. Cependant, le dépistage de la cirrhose est encore insuffisant, le retard à l’admission excessif, et l’antibio-prophylaxie devrait être systématique.
Introduction

Gastrointestinal hemorrhage is a serious complication of cirrhosis. Management practices have been greatly improved over the last twenty years and have led to a significant reduction in related mortality in France [1] and other western countries [2-5]. Several consensus workshops have established guidelines for good clinical practices [6, 7]. The first French Consensus Workshop held in Paris in December 2003 was devoted to the main complications of portal hypertension in adults and focused particularly on the prevention and treatment of gastrointestinal hemorrhage related to cirrhosis. The workshop guidelines were published in this journal [8]. As emphasized in a recent editorial [9], guidelines for good clinical practice should be evaluated. It has been demonstrated that nearly half of patients with chronic disease, irrespective of the cause, receive insufficient care despite scientific proof of the efficacy of the proposed treatments [10]. Regarding portal hypertension, the literature is scarce [11-14], and generally illustrates wide variability in management practices. Current practices, which a greatly depend on the center, underuse beta-blockers for primary prevention of hemorrhage, even when the diagnosis of cirrhosis is known. Furthermore, despite the major prognostic impact of early treatment, none of the reported surveys have examined the time delay to care [15].

The main purpose of this before-after observational study was to assess practices used for the management of gastrointestinal hemorrhage related to portal hypertension in patients with cirrhosis and the impact of the French guidelines. This survey was also conducted to search for factors explaining non-compliance with the guidelines.

Patients and methods

This prospective questionnaire survey was conducted from September 1st to November 30th 2003, i.e. before the consensus workshop, and again during the same period in 2004, after the workshop. This survey was proposed to hepatogastroenterologists in 31 general and university hospitals in five regions in France (Aquitaine, Champagne-Ardennes, Pays-de-Loire, Picardie and Poitou-Charentes) and in two other administrative districts (Oise and Val-d’Oise). These five regions and these two administrative districts were selected as follows: an investigator, member of the national working group on portal hypertension was asked to recruit all general and university hospitals in his/her region or administrative district to participate in this survey. The present analysis retained uniquely those centers which participated in both surveys.

Patients with an episode of gastrointestinal hemorrhage were included if they had clinical cirrhosis or histological proven cirrhosis, irrespective of the cause, and if their hemorrhage was considered to be linked with portal hypertension. Patients were not included if they presented hemorrhage unrelated to portal hypertension, or if the portal hypertension was not related to cirrhosis. The following data items were collected with an anonymous questionnaire: birth date, residence, mode of admission, cause of hemorrhage and its severity, date of admission, recurrence of hemorrhage during the survey period, complications of cirrhosis developing during the observation period. The severity of cirrhosis was assessed with the Child-Pugh score [7] established at admission [16]. Data were collected relative to the index episode, which corresponds to the first hemorrhagic episode during the survey period. Later episodes were recorded but the management practices were not considered for this analysis. Use of erythromycin for gastric emptying before the hemorrhage was defined as any episode of bleeding occurring between 48 hours of the index episode and day 42. Mortality was assessed on day 42. In the European literature from 1993 to 1996, the incidence of upper gastrointestinal hemorrhage was estimated at 45 to 143/105 inhabitants, depending on the country, with an incidence of esophagogastric variceal rupture in 5-13.7% of the cases, i.e. 4 to 19.6/105 inhabitants [17-19]. Thus, considering the population in the geographical recruitment of this survey, a period of three consecutive months was considered necessary to obtain 100 cases eligible for analysis per period.

Management practices applied for patients presenting gastrointestinal hemorrhage before and after the Paris Consensus Workshop were compared using the chi-square test or Fisher’s one-way analysis, accepting an alpha risk of 0.05. Two-way univariate analysis, using the chi-square test or Fisher’s test as appropriate, was applied to search for factors linked with compliance with management guidelines. Stepwise multivariate logistic regression analysis was then applied to variables with a P<0.20. Besides the year of study, factors studied included patient characteristics (age, gender, distance from residence to center), disease (known cirrhosis, Child-Pugh class, history of hemorrhage), circumstances (transportation by emergency squad, hour of admission), and healthcare region.

This study was approved by the Consultative Committee for Information Processing concerning research in the field of health care.

Results

Five university hospitals and fifteen general hospitals agreed to participate in the two surveys. Data from eleven other centers which did not participate in the first survey before the Consensus Workshop were not retained for analysis. In 2003, 76 patients, mean age 59±13 years (61 men and 15 women) were included and in 2004, 84 patients mean age 59±13 years (62 men and 22 women). The characteristic features of the patients and outcome at 42 days are summarized in table I. Etiologies of cirrhosis were comparable for the two surveys, but the severity of cirrhosis was different, with a larger proportion of Child-Pugh C patients in 2003 (49%) compared with 2004 (28%) (P=0.009). Patient history — early episodes of hemorrhage, primary prophylaxis, secondary prophylaxis before the index episode — are presented in table II. Nearly half of the first hemorrhagic epi-

Table I. — Patient characteristics and outcome for the two surveys.

<table>
<thead>
<tr>
<th>Etiology of cirrhosisa N (%)</th>
<th>2003 survey (N=76)</th>
<th>2004 survey (N=84)</th>
<th>P (two-way)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
<td>61 (85)</td>
<td>63 (79)</td>
<td></td>
</tr>
<tr>
<td>viral hepatitis (B, C)</td>
<td>5 (7)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>alcohol and another cause</td>
<td>3 (4)</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh score (A/B/C) (N)</td>
<td>18/19/36b</td>
<td>20/39/23b</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Outcome: N (%)

| — Recurrent hemorrhage between 48h and day 42 | 13/69 (19) |
| — Mortality at day 42 | 11/71 (15) |

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and 2004. Multivariate analysis demonstrated that patients who presented to the emergency team in 44 and 36% of cases respectively in 2003 and 2004. There was no evidence of significant improvement in time to admission for patients with recurrent hemorrhage (P=0.17) nor for patients with Child-Pugh C cirrhosis (P=0.61). The patient was transported to hospital by the emergency squad (P=0.061; OR=0.47; 95% CI=[0.21-0.93]) and were admitted at night (P=0.014; OR=0.36; 95% CI=[0.16-0.81]).

Vasoactive treatment (octreotide for 88% and 91% of patients vs 76% in 2004. This antibiotic therapy was prescribed for documented or suspected infection in about 8% of patients in both surveys. Antibiotic prophylaxis was instituted more often in 2004 (70% vs 61% in 2003, P=0.098), with significant variability by geographic region (from 47% to 88% of patients, P=0.030). Multivariate analysis showed that antibiotic prophylaxis was prescribed less often in Child-Pugh A patients (P=0.044; OR=3.59 with 95%CI=[1.32-9.79]).

The rate of recurrent bleeding during follow-up (48 h to day 42) was unchanged from 2003 to 2004 (17% vs 19%). Mortality was not different between the two periods (15% vs 10%).

### Discussion

This study demonstrates that one year after the first French Consensus Workshop on the complications of portal hypertension held in Paris in December 2003, management practices in France for patients with cirrhosis-related gastrointestinal hemorrhage generally complied with the published guidelines [8]. A general improvement in practices was noted, yet certain recommendations were insufficiently applied.

Although gastrointestinal bleeding is considered a life-threatening complication, hospital admission often occurred late, more than 12 hours after onset of bleeding in nearly 40% of patients and despite the fact that in France the general population resides less than one hour from a hospital center. Time to hospitalization was not shorter in patients with more severe bleeding or who had already had a prior episode, illustrating the lack of awareness of both patients and physicians concerning the gravity of this complication. Mean time from admission to endoscopy was 4.5 hours, a reasonable delay which was unchanged after publication of the guidelines. Vasoactive treatment was instituted early.

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### Table II

- **Prevention of gastrointestinal hemorrhage related to portal hypertension before occurrence of the index hemorrhagic episode.**

<table>
<thead>
<tr>
<th></th>
<th>2003 survey (N=75)</th>
<th>2004 survey (N=83)</th>
<th>P (one-way)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First bleeding episode, N (%)</td>
<td>43 (57)</td>
<td>43 (52)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis known at admission:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Endoscopy to screen for esophageal varices</td>
<td>20/43 (47)</td>
<td>23/41 (56)</td>
<td>0.030</td>
</tr>
<tr>
<td>— Stage 2-3 varices:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— β blockers</td>
<td>6 (10)</td>
<td>10 (14)</td>
<td></td>
</tr>
<tr>
<td>— Endoscopic sclerosis</td>
<td>2 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>— Ligature and β blockers</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Recurrent hemorrhage, N (%)</td>
<td>32 (43)</td>
<td>40 (48)</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis before admission:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— None</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>— Endoscopic sclerosis</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>— Ligature</td>
<td>6 (19)</td>
<td>16 (42)</td>
<td></td>
</tr>
<tr>
<td>— β blockers</td>
<td>13 (41)</td>
<td>14 (37)</td>
<td>0.018</td>
</tr>
<tr>
<td>— Combination ligature/sclerosis and β blockers/nitrates</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Missing data: early death in one patient in 2003 and data unavailable in one patient in 2004.*
Management practices for gastrointestinal hemorrhage related to portal hypertention in cirrhotic patients

in nearly all of the patients, with a significantly shorter delay in 2004, in agreement with the guidelines. It can be estimated that because of early control of the bleeding, the endoscopy procedure, which was generally deferred, was performed under better technical conditions after hemodynamic stability had been achieved. For preparation, erythromycin replaced the classical gastric aspiration, again in application of the guidelines. During the initial endoscopy, elastic variceal ligature was the standard treatment, sclerosis has almost been abandoned.

It is more difficult to analyze application of the recommendations concerning blood transfusion since hematocrit values were collected only at admission. Nevertheless, few patients with a hematocrit above 30% were transfused without clinical signs of hemodynamic shock. Antibiotic prophylaxis was much more common after publication of the guidelines, yet despite the fact that a meta-analysis has demonstrated a significant impact on survival [20], antibiotics were not used for more than one quarter of the patients. Antibiotic prophylaxis was proposed preferentially for patients with the most severe bleeding, who effectively had the greatest risk of infection [21] but this specific distinction was not stated in the guidelines. Surprisingly, prevention of encephalopathy with lactulose was significantly more frequent in 2004 despite the fact that the workshop specifically recalled its lack of efficacy in this situation. The biggest surprise was the progress made in the use of β-blockers given alone for secondary prevention and the unexpected constant use of β-blockers with endoscopic ligation. This increasingly popular combination was first proposed by the French guidelines but had not been retained in the earlier Baveno III guidelines [7].

This type of survey cannot avoid the usual biases of observational data collection. The participating centers were not randomly selected, the survey was not conducted by independent observers, and the short duration of the study limited the number of patients. Nevertheless, the geographic distribution of the participating centers with a logical proportion of general and university hospitals of various sizes and expertise as well as the heterogeneous nature of the results show that there is no clear evidence that practices were strictly dictated by the published guidelines. Similarly the second survey failed to demonstrate any dramatic improvement, suggesting that the center sample was reasonably representative of routine practices in France and that the investigators avoided overt bias.

This assessment of routine practices identified a certain number of priorities. Cirrhosis was revealed by gastrointestinal hemorrhage in nearly one half of the patients, illustrating the insufficient screening for cirrhosis in France. Widespread use of noninvasive tests for fibrosis could improve this situation. Conversely, there was a clear progress in endoscopic screening for large-sized esophageal varices in patients with known cirrhosis. In surveys of practices in the United States, Arguedas et al. [11]
noted that only half of patients with cirrhosis referred for assessment prior to proposed liver transplantation had undergone endoscopic screening for portal hypertension. In the two surveys reported, all patients had not been given primary prophylaxis even if they had large varices. Sorbi et al. [12] also noted in 1997 that primary prevention with β-blockers was insufficient since only 20-30% of patients were treated before onset of bleeding. The 1997 recommendations of the American College of Gastroenterology were however applied since 54% of gastroenterologists, i.e. three times more than those questioned before the recommendations, stated three years later they screened for esophageal varices and prescribed prophylaxis to prevent primary rupture [14].

Information delivery to patients at risk and to medical teams providing care for patients with gastrointestinal hemorrage remains insufficient. Patients with cirrhosis should be better informed about the risk of bleeding. Besides the classical risk of shock or hematemesis, patients should be advised that anemia with major tiredness and especially melena are important signs which should prompt rapid admission to a specialized center. In this survey, emergency team transportation was used more often in 2004 for patients with less severe cirrhosis than in 2000. The usefulness of early prehospital care before and during transport has been emphasized by a French team [22]. Hepatogastroenterologists are of course just one link in the health care chain, probably explaining the wide variety of practices between centers, especially concerning antibiotic prophylaxis. Care protocols should be established in cooperation with emergency care and intensive care units. The Consensus Workshop guidelines should be distributed in a pocket-sized brochure or published on the hospital intranet for easy access.

Conclusion

The Consensus Workshop guidelines clearly contributed to improved clinical practices. Limitations were related to insufficient screening for cirrhosis, overly long delay to admission, and insufficient use of antibiotic prophylaxis, which should become systematic. The guidelines should be distributed more widely, particularly for patients at risk and for clinicians implicated in their emergency management.

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