Medical treatment of portal hypertension

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Abstract

Prevention of the first variceal haemorrhage should start when the patients have developed medium sized to large varices. Non-selective beta-blockers are the first-line treatment ; band ligation is roughly equivalent to beta-blockers and is the first choice for patients with contraindications or intolerance to beta-blockers.

Treatment of acute bleeding should aim at controlling bleeding and preventing early rebleeding and complications, especially infections. Combined endoscopic and pharmacological treatment with vasoactive drugs can control bleeding in up to 90% of patients.

All patients who survive a variceal bleed should be treated with beta-blockers or band ligation to prevent rebleeding. All patients in whom bleeding cannot be controlled or who continue to rebleed can be treated with salvage TIPS or, in selected cases, with surgical shunts. Liver transplantation should be considered for patients with severe liver insufficiency in which first-line treatments fail. (Acta gastroenterol. belg., **2004**, 67, **334-343**).

Key words : variceal bleeding ; vasoactive drugs, endoscopic sclerotherapy, beta blockers, TIPS, meta-analysis, odds ratio, number needed to treat, confidence intervals.

Introduction

Variceal bleeding carries a mortality which, in the most recent studies, ranges around 20% (1,2) ; in addition, a patient surviving a variceal bleed has a risk of rebleeding, if untreated, of about 60% (3). Therefore, therapeutic strategies for portal hypertension must include measures to prevent the first bleed, to treat acute bleeding and to prevent rebleeding.

In order to prevent variceal formation, growth and rupture, several approaches can be considered. Portal pressure may be reduced by drugs that decrease portal venous inflow, such as vasoconstrictors (acute administration of terlipressin, somatostatin or its analogues for acute bleeding, long term treatment with non-selective beta blockers to prevent first bleeding and rebleeding), or by drugs that decrease intrahepatic resistance, such as vasodilators (isosorbide-5 mononitrate). A greater reduction in portal pressure can be obtained by a combination of vasoconstrictors and vasodilators, which decreases both portal flow and intrahepatic resistance (4). An even greater reduction in portal pressure may be achieved by surgical or radiological shunt interventions, which divert the portal blood into the systemic circulation. Finally, variceal bleeding may be prevented by endoscopic treatments aimed at obliterating the varices, which, although not influencing portal pressure, decrease the risk of bleeding by closing the varicose channels. In this review, I will analyse the possible strategies to prevent and treat esophageal variceal rupture.

Preventing the first variceal haemorrhage

Longitudinal studies have shown that varices eventually develop in the majority of cirrhotic patients (5,6), and that once they have developed, they tend to increase in size and to bleed (6). The rate of development of new varices varies between 5 and 12% per year (5,7), with rare exceptions (8), while the rate of growth of varices from small to large ranges between 6 and 70% at 2 years (9-11). The prevention of the first variceal bleed (primary prophylaxis) could therefore aim at : a) preventing variceal formation, or b) preventing the growth of small to large varices, or c) preventing the rupture of medium-large varices.

The prevention of variceal formation has been attempted in two studies, in which beta-blockers were used. In the first one (12), 208 patients, of which 38% had no varices at enrolment, were randomized to placebo or propranolol treatment. At 2 years of follow-up, significantly more patients on propranolol (31%) had developed large varices as compared with patients on placebo (14% ; $p < 0.05$). There was no difference in the development of large varices in patients with no varices or with small varices at inclusion. The proportion of patients who bled from varices (2%) was identical in the two groups. This study has been criticized because no measurement of portal pressure was done and there was a 35% overall dropout rate. The second study (6) enrolled 213 patients with no varices and proven portal hypertension (HVPG > 6 mmHg), which were randomized to placebo or timolol. At 4 years of follow-up, 37% of patients developed esophageal varices and 3% bled, with no difference between the study groups. The number of serious adverse events was significantly higher in patients treated with timolol (19% vs. 6% ; $p < 0.01$). From the above data, it appears that beta-blockers treatment is not effective in preventing the development of varices in patients with portal hypertension.

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The prevention of the growth of small varices to large ones has been investigated in two studies, the French one mentioned above (12), in which propranolol was ineffective in preventing the growth of varices in the 62% of patients with small varices at enrolment, and an Italian trial (14), in which 161 patients with small varices were randomized to receive either nadolol or placebo. At 3 years, the varices had increased in size in 11% of patients in the nadolol group and in 37% of those receiving placebo ($p < 0.01$). Significantly fewer patients bled in the nadolol group (2.4%) than in the placebo group (11.5% ; $p = 0.022$). Thus, two studies of similar design gave opposite results. as a consequence, no definitive conclusion can be drawn on the efficacy of beta-blocker treatment in preventing the enlargement of varices.

As far as the prevention of the rupture of medium-large varices is concerned, in the 1980s, both non-selective beta-blockers and endoscopic sclerotherapy were studied as possible treatments for prevention of first bleeding. Sclerotherapy has been subsequently abandoned because of inconsistency of results across trials (15,16), while beta-blockers have become the mainstay of prophylaxis (17,18). It is generally agreed that only patients with medium-sized or large varices should be treated prophylactically (18,19), since the risk of bleeding in patients with small varices is very low (19). A recent meta-analysis (19) of trials comparing beta-blockers with placebo showed that beta-blockers reduce the mean weighted incidence of bleeding from 25% to 15%, with a relative risk reduction of 40% and an absolute risk reduction of 10% (95% confidence intervals -16% to -5%). This means that 10 patients must be treated with beta-blockers to prevent one bleed that would have occurred if all patients had been treated with placebo (Number needed to treat –NNT- = 10). Patients in whom beta-blockers decrease the HVPG to below 12 mmHg are completely protected from bleeding (20), while a reduction of 20% from baseline values reduces the incidence of bleeding to less than 10% (21). Unfortunately, a reduction below 12 mmHg or a 20% decrease of the HVPG from baseline can only be achieved in about 20% and 35% of patients respectively. In addition, beta-blockers cause side effects in 16-20% of cases, which lead to the withdrawal of 6-12% of patients from therapy (22-24).

These facts have stimulated the search for alternative strategies for preventing first bleeding. Nitrovasodilators have been investigated for their ability to decrease portal pressure by decreasing hepatic and portocollateral resistance. In one study (25), isosorbide-5-mnonitrate was equivalent to propranolol in preventing bleeding, but, on extended follow-up (26), was associated with a significantly higher mortality in patients over 50 years of age. In a study in decompensated cirrhotic patients (27), isosorbide-5-mononitrate had significantly fewer side effects as compared to nadolol, but was significantly less effective in preventing bleeding. A third study comparing isosorbide-5 mononitrate with placebo in patients with intolerance or contraindications to beta-blockers (28) showed no difference between treatments for the prevention of bleeding. Experimentally, combination therapy with isosorbide-5-mononitrate and beta blockers has been shown to enhance the portal pressure lowering effect of beta blockers (4). This combination has been compared with beta-blockers alone in three studies (29-31). Meta-analysis of these studies (19) showed no significant difference in efficacy between treatments, while side effects were remarkably more frequent with the combination therapy. Thus, isosorbide 5-mononitrate, alone or in combination with beta-blockers, does not appear to be a suitable alternative to beta-blockers for prevention of the first variceal bleeding.

In recent years, band ligation has been compared with no treatment in five trials (32-36). Meta analysis of these studies (37) has shown that band ligation significantly decreases both the incidence of first bleeding and mortality. A comparison between band ligation and beta-blockers has been made in eight trials (38-45, Fig. 1), only 3 of which (39,42,45) are published in full. In all studies, band ligation was more effective than beta-blockers in preventing first bleeding, but the difference reached statistical significance only in 2 (39,43). Meta-analysis of these trials (46) shows that band ligation reduces the incidence of first bleeding from 24.6 % to 12.7%, with a relative risk reduction of 48%, an absolute risk reduction of 11.9% (95% confidence intervals -16% to -4%) and a number needed to treat of 8.4 (Fig. 2A). Mortality was equal with the two treatments. It has been argued that in the only two trials that showed a significant difference in favor of band ligation (39,43), the performance of beta-blockers was exceedingly poor. In effect, when these two trials are excluded from meta-analysis, the difference is greatly reduced (Fig. 2B ; bleeding : beta-blockers 22%, band ligation 13%, relative risk reduction 39% ; absolute risk reduction 9% (95% C.I. -12.6% to + 0.009% ; number needed to treat 11.1) (46). Thus, band ligation is at least as effective as beta-blockers in preventing the first variceal bleeding.

A recent study has investigated the value of tailoring pharmacological treatment according to the HVPG response to beta-blockers (47). In that study, nonresponders to propranolol received additional I5Mn. None of the patients who responded to propranolol alone or to propranolol + I5Mn bled, as compared to 33% of nonresponders. This approach deserves further testing. It appears thus that prevention of first variceal bleeding should start when patients have medium-sized or large varices. Beta-blockers remain the mainstay of treatment, while band ligation should be the first-line treatment for patients with contraindications or intolerance to beta-blocker treatment (l) (Fig. 3). Cost-effectiveness analyses should be made to clarify whether band ligation can be used as an alternative to beta-blockers for all patients. Whether the tailoring of pharmacological treatment based on HVPG monitoring is really worthwhile should be verified in larger patient's series.

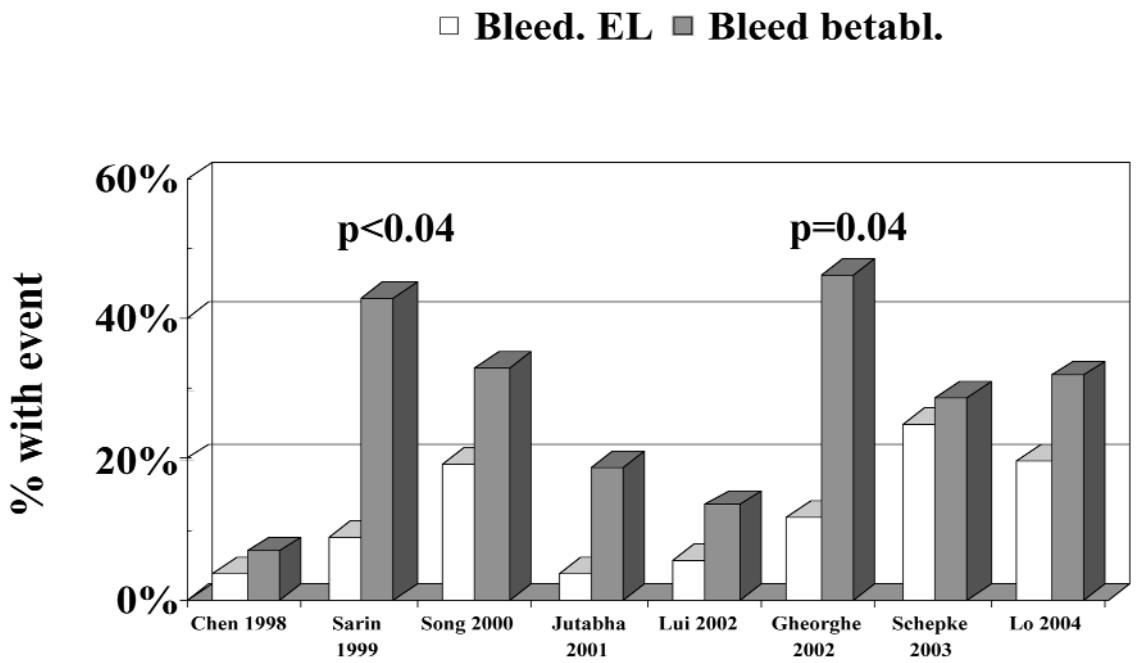

Fig. 1. — Randomized Controlled Trials of Endoscopic Ligation (EL) vs. Beta-blockers for the prevention of the first variceal bleed

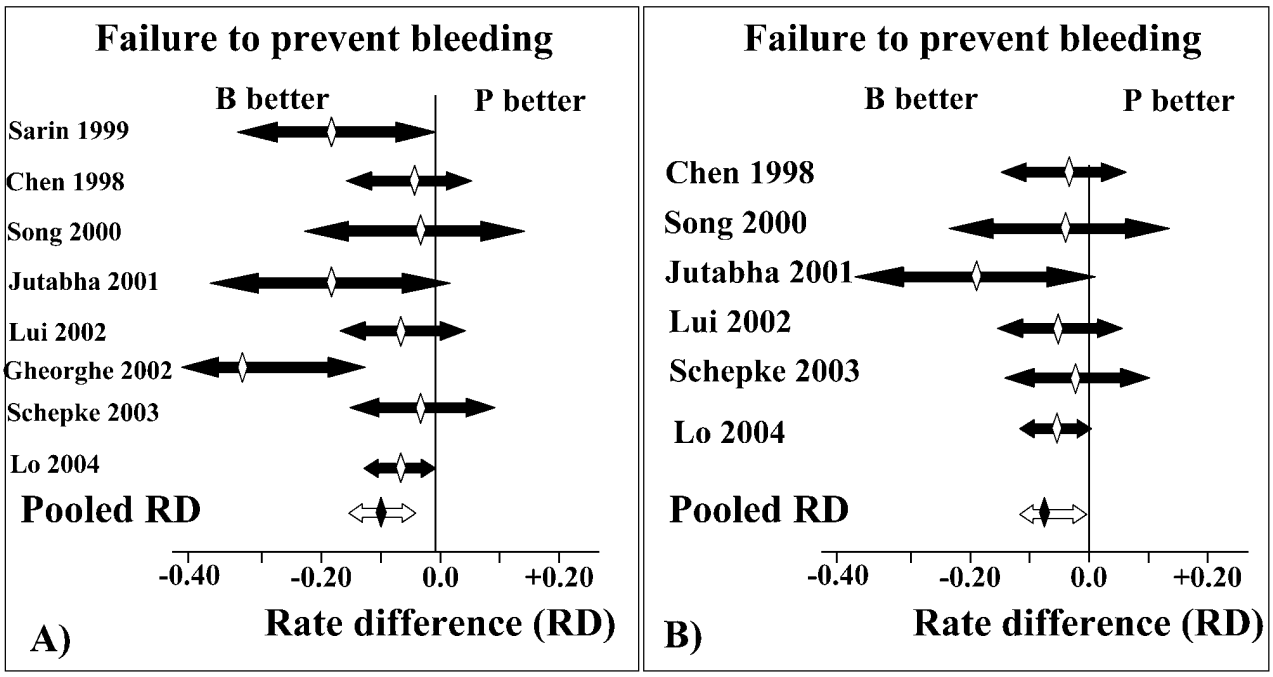

Fig. 2. — Meta-analysis of randomized controlled trials of primary prophylaxis of variceal haemorrhage : band ligation (B) vs. propranolol (P). A) : all studies ; B) : excluding Sarin's and Gheorghe's trials.

Treating acute bleeding and preventing early rebleeding

Variceal bleeding is a life-threatening complication of portal hypertension which, in spite of recent progress (48), still carries a high mortality (1,2) and has substantial resource-use implications (49). Mortality is related to several factors such as failure to control bleeding, early rebleeding, the severity of the underlying liver disease, the presence of infection and of disease in other systems. The management of the acute bleed is a multistep process that includes the initial assessment of the patient, effective resuscitation, timely diagnosis, control of bleeding and prevention of early rebleeding and

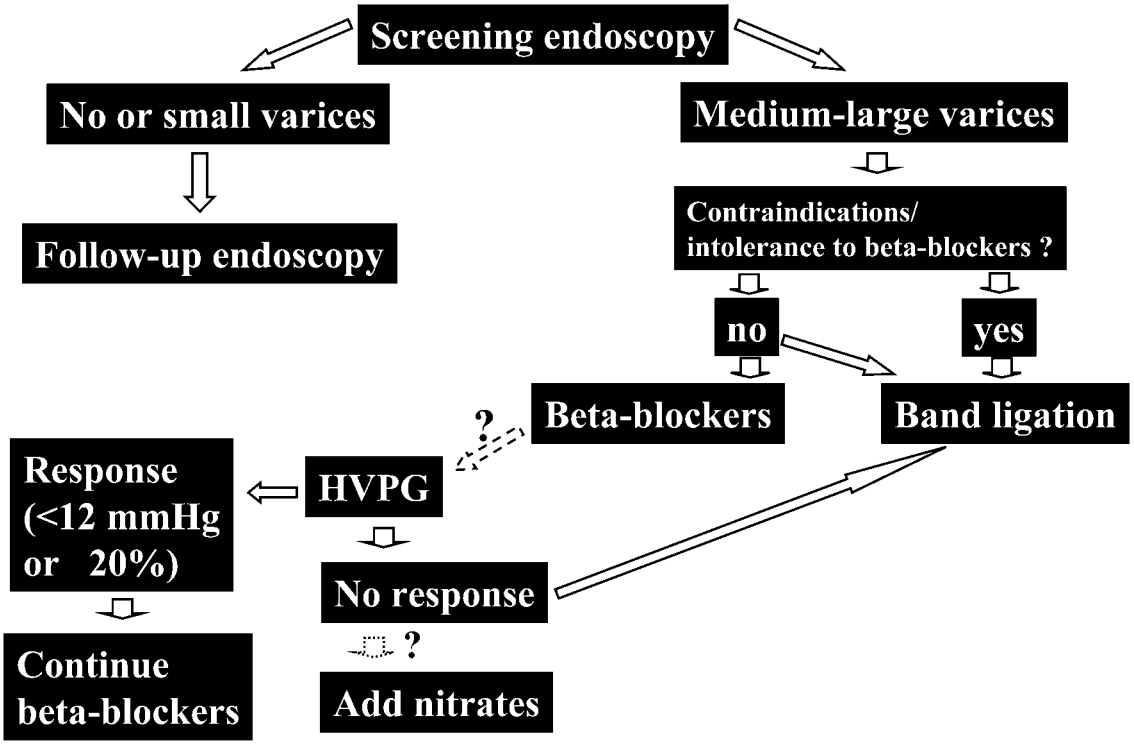

Fig. 3. — Algorithm for prevention of first variceal bleeding in cirrhosis. Dotted arrows with question marks denote steps that need to be verified.

complications such as infection, renal failure or hepatic encephalopathy. It has been recently shown that about 2/3 of deaths in which bleeding is the precipitating cause occur within 24 hours of the onset of bleeding, thus emphasizing the need to act fast and decisively as soon as the patient reaches the hospital (50).

Treatment of acute variceal bleeding should aim both at controlling bleeding and at preventing early rebleeding, which is particularly common within the first week and is associated with increased mortality (51). Both pharmacological therapy with vasoactive drugs (terlipressin, somatostatin, octreotide) (19) and endoscopic treatment (sclerotherapy and band ligation) (16) have been shown to be effective in controlling acute bleeding. Studies comparing endoscopic sclerotherapy and pharmacological treatment with vasoactive drugs have shown that the two treatment modalities have similar efficacy, while sclerotherapy has a somewhat higher complication rate (52,53). A recent study from Spain (54) compared different schedules of somatostatin administration. A retrospective analysis of the data suggested that a double dose of somatostatin infusion (500 µg/hour) may be more effective than the standard 250 µg/hour dose in patients with active bleeding at endoscopy. This finding will have to be confirmed in prospective studies.

Treatment regimens combining the use of a vasoactive drug (terlipressin, somatostatin or its analogues octreotide or vapreotide) with endoscopic therapy (sclerotherapy or band ligation) have received a great deal of attention in recent years. Between 1995 and 2001, 10 studies (55-64), including a total of 1273 patients, have compared combined treatments with endoscopic treatments alone. A recent meta-analysis (65) including eight of these trials (56-59,61-64) showed that pharmacological + endoscopic treatment is more effective than endoscopic therapy alone in controlling acute bleeding and preventing 5 days rebleeding, while there was no difference in mortality. Even including the studies that were excluded (55,60) or only partly included (59) in this meta-analysis, the results do not change [control of acute bleeding : combination 90% ; endoscopic treatment alone 76% ; relative risk reduction 16% ; absolute risk reduction 14% (95% confidence intervals + 4% to + 23%), NNT = 7 ; 5-days prevention of rebleeding : combination 72% ; endoscopic treatment alone 59% ; relative risk reduction 18% ; absolute risk reduction 13% (95% confidence intervals – 8% to – 17%) ; NNT = 7.7]. There was no difference in 5-day and 42-day mortality figures (combination 7% ; endoscopic treatment alone 9% at 5 days ; 22% and 27% respectively at 42 days) (Fig. 4). The combination of emergency sclerotherapy plus somatostatin or octreotide infusion has been compared with somatostatin or octreotide alone in two trials (66,67). In both, the combined treatment was more effective than drug treatment alone in controlling bleeding and preventing early rebleeding, although statistical significance was only reached in the first one. It

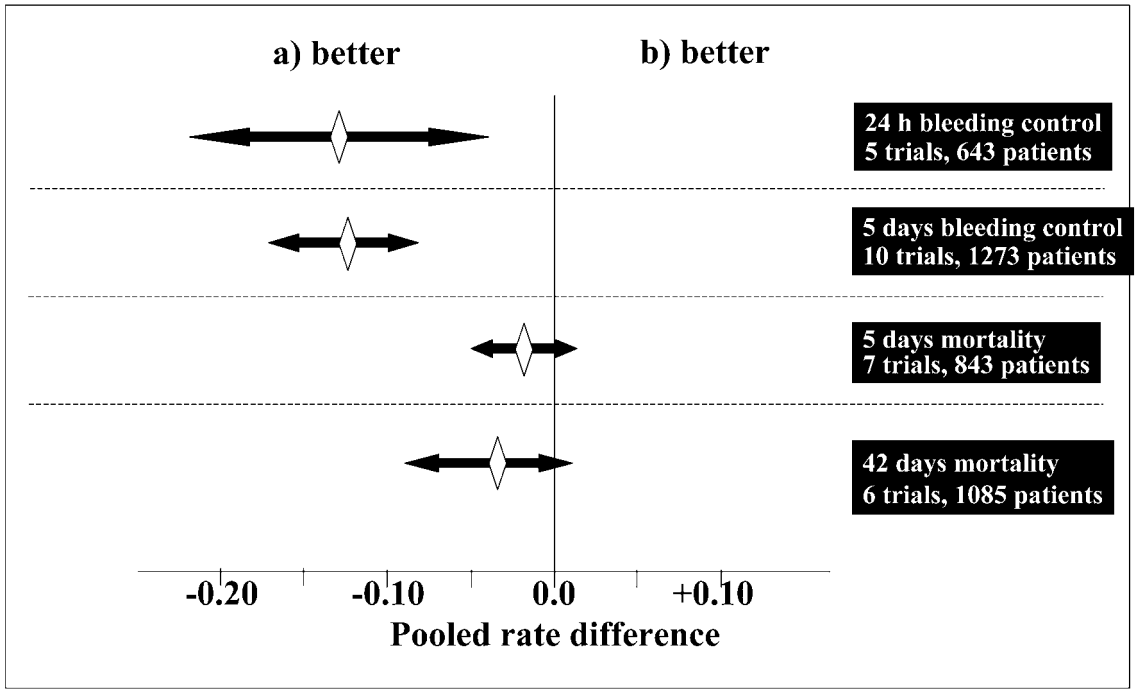

Fig. 4. — Meta- analyses of treatments for acute bleeding in cirrhosis : drugs + endoscopic treatments (a) vs. endoscopic treatments alone (b). (10 trials ; 1273 patients).

appears thus that the combination of endoscopic and pharmacological treatment can control bleeding in about 90% of patients and prevent early rebleeding in about 80% (65). A recent survey has shown that this combination is widely adopted in the routine management of variceal bleeders (1).

It has recently been shown that the administration of recombinant activated factor VII (rFVIIa) normalizes prothrombin time in bleeding cirrhotics (68). The potential role of rFVIIa has been evaluated in a multicenter European trial (69), including 245 bleeding cirrhotic patients who were randomized to receive 8 doses of rFVIIa,100 µg/Kg or placebo in addition to combined endoscopic + pharmacological treatment . The primary endpoint was a composite including : failure to control bleeding at 24 hours, failure to prevent rebleeding between 24 hours and 5 days, and death within 5 days. No significant effect was found when analyzing the whole patients population ; however, an exploratory analysis showed that, in Child-Pugh B and C variceal bleeders, rFVIIa significantly reduced the occurrence of the primary endpoint (from 23% in patients receiving placebo to 8% in patients receiving rFVIIa, $p = 0.03$), and improved bleeding control at 24 hours (from 88% to 100%, $p = 0.03$). These data are encouraging, but require confirmation by studies specifically targeted on the appropriate patients.

Bacterial infection is a serious complication of advanced cirrhosis, particularly in bleeding patients (70-74). The urinary tract, ascites, respiratory tract, or multiple sites may be involved (72), with spontaneous bacterial peritonitis accounting for 7-12% (71,72) ; the enteric flora accounts for the majority of infections, and E. Coli is the most frequently involved pathogen. Infections have been reported to occur in over 1/3 of bleeding cirrhotic patients (70) within 7 days of admission, and are associated with failure to control bleeding (73), early rebleeding (70) and early death (73). It has been postulated that infection may impair coagulation, thus facilitating failure to control bleeding and early rebleeding (75,76). Eight trials have evaluated the efficacy of antibiotic prophylaxis in bleeding cirrhotic patients : two meta-analyses, including 5 (73) and 8 (74) trials respectively, have shown that antibiotic prophylaxis is effective in preventing infection and increasing survival. Thus, antibiotic prophylaxis has become an integral part of the management of bleeding cirrhotic patients (18). When different antibiotic regimens were compared, no specific regimen showed superiority over other regimens in preventing infection or improving survival (78).

Even in the best situation, the current therapies fail to control bleeding or to prevent early rebleeding in about 8-12% of patients, who must be treated by alternative means. In principle, emergency shunt surgery and the transjugular intrahepatic porto-systemic stent shunt (TIPS) appear as appropriate therapies ; however, since the majority of these patients have severe liver insufficiency (Child-Pugh class C), TIPS is probably the best option. To date, TIPS has been used as a salvage treatment in patients failing first-line therapy in 15 studies (79), including 509 patients, 64% of whom where

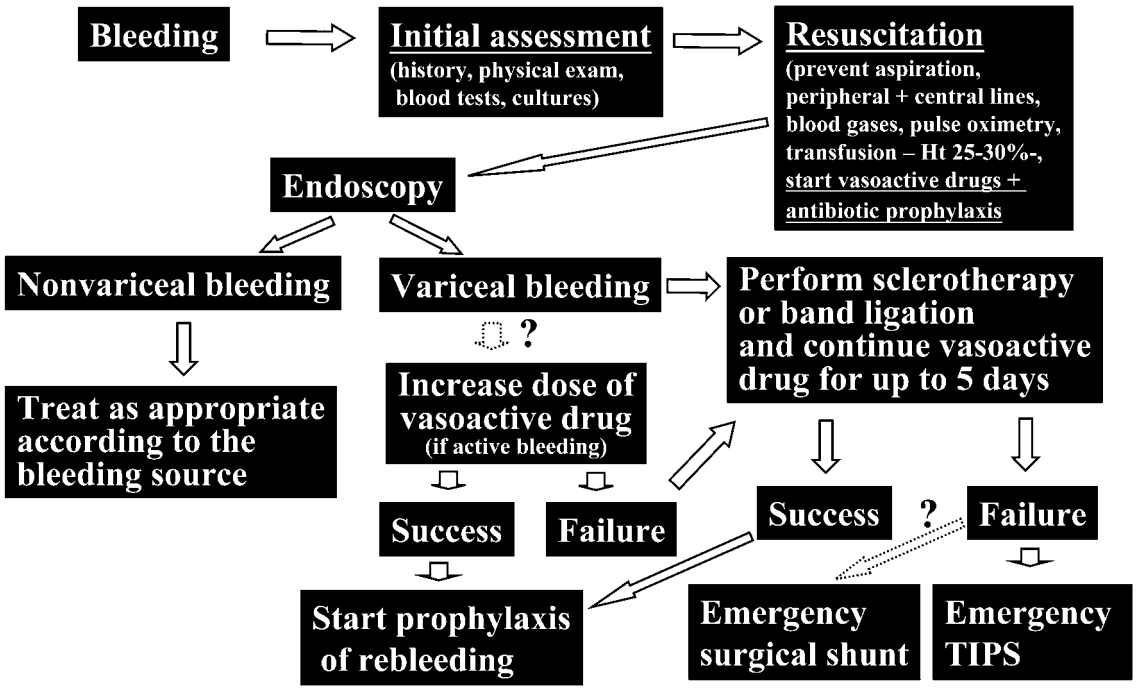

Fig. 5. — Algorithm for treatment of acute variceal bleeding in cirrhosis. Dotted arrows with question marks denote steps that need to be verified.

Child-Pugh Class C. Overall, immediate control of bleeding was achieved in 94% of patients (range 75-100%) ; 10 studies give figures for rebleeding, with a mean of 11.4% (range 6-27%) at 7-30 days, while 30 days mortality was 31.9% (range 15-75%). Although none of the studies is a randomized trial, and only one is a retrospective comparison with an alternative surgical therapy (80), these results strongly suggest that emergency TIPS is a valid salvage procedure for patients failing first-line endoscopic and pharmacological treatment (18).

In conclusion, the management of acute bleeding should include a careful assessment of the patient, to evaluate both the severity of the bleeding and of the underlying cirrhosis. Resuscitation should include measures to avoid aspiration, monitoring of blood gases and pulse oximetry ; transfusions should be made cautiously to avoid overshoot in portal pressure ; antibiotic prophylaxis and treatment with vasoactive drugs should be started early, and the latter should be continued for up to 5 days. Endoscopy should be done as soon as the patient can tolerate it ; either sclerotherapy or band ligation can be used as haemostatic treatments. The value of increasing the dose of vasoactive drugs in active bleeders and of adding rFVIIa in Child-Pugh B and C patients needs further evaluation in appropriately designed trials. For patients failing combined vasoactive and endoscopic therapy, emergency TIPS appears to be an effective salvage therapy ; surgical shunts may be indicated in good risk patients, while the feasibility of liver transplant should be considered for patients with severe liver failure (18). Figure 5 shows an algorithm for the management of acute variceal bleeding based on the above recommendations.

Preventing late rebleeding

If left untreated, patients surviving a variceal hemorrhage have median risks of rebleeding and of death of 63% and 33% respectively (15). Given these figures, the current recommendation is to treat all patients to prevent rebleeding (81). In principle, rebleeding could be prevented by surgical shunts, drugs, endoscopy and TIPS.

Surgical shunts have largely been used in the 1960s and 1970s, but have subsequently been almost abandoned, although some recent study showed good results with the small diameter prosthetic H-graft portacaval shunt (82). Therefore, nowadays the majority of patients are treated with drugs or by endoscopy.

Beta-blockers are more effective than placebo in preventing rebleeding and death (19) [average rebleeding rate : placebo : 63% ; beta-blockers 42%, relative risk reduction 33% ; absolute risk reduction 21% ; (95% confidence intervals -30 to – 13) NNT = 4.76 ; mortality : placebo 27% ; beta-blockers 20% ; relative risk reduction 26% ; absolute risk reduction 7% (95% confidence interval -12 to -2%) ; NNT 14.2].

Thirteen studies have been performed comparing ligation with sclerotherapy. Meta-analysis of these trials (16) shows that band ligation is significantly more

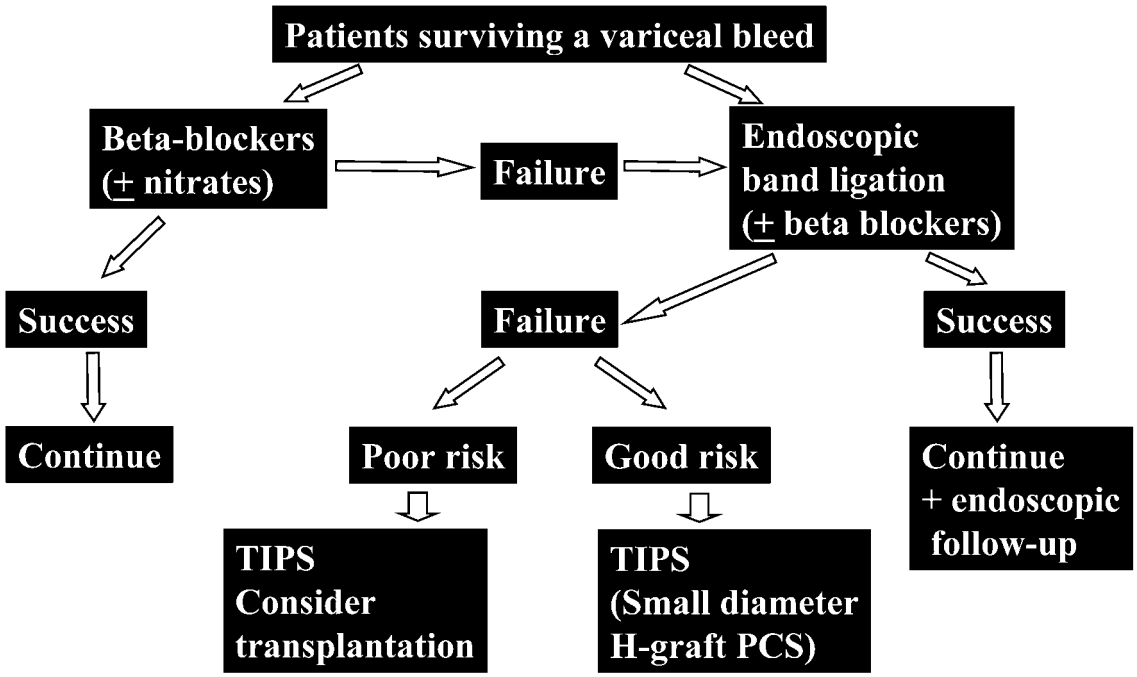

Fig. 6. — Algorithm for the prevention of variceal rebleeding in cirrhosis

effective than sclerotherapy in preventing rebleeding, [banding 22%, sclerotherapy 35% ; relative risk reduction 37% ; absolute risk reduction 13% (95% confidence intervals -18% to -6%) ; NNT = 8], while there is no difference in mortality (22 vs. 25%). As a consequence, band ligation is now the recommended endoscopic therapy to prevent variceal rebleeding (18). Recently, a medical regimen of beta-blockers + isosorbide-5-Mononitrate has been compared with sclerotherapy in one trial (83) and with band ligation in 3 (84-86). The combined medical treatment was superior to sclerotherapy in preventing rebleeding, with no difference in mortality (83), while the 3 trials in which band ligation was used gave conflicting results : the medical regimen was significantly better than banding in preventing rebleeding in one (84), significantly worse in the second (85), while the third showed no difference between treatments (86) (Table 2) None of the trials showed a difference in mortality. Meta-analysis of these studies shows no difference between treatments in preventing rebleeding [medical treatment : 37.5% ; banding 40% ; relative risk reduction 6.25% ; absolute risk reduction 2.5% (95% confidence intervals -23% to + 3%) ; NNT = 40] and death [medical treatment : 26% ; banding 34% ; relative risk reduction 24% ; absolute risk reduction 8% (95% confidence intervals -1 to + 17%) ; NNT = 12.5] (Table 2). However, this conclusion should be interpreted with caution, since the number of patients included in the trials is relatively small. Therefore, the question whether medical treatment with beta-blockers + isosorbide mononitrate is better than band ligation or vice-versa is still open. A single trial (87) compared a combination of band ligation, beta blockers and sucralfate with band ligation alone, showing that the combined therapy was better than ligation alone in preventing rebleeding and variceal recurrence. These data need confirmation.

In 11 studies, TIPS has been compared with endoscopic therapy for the prevention of variceal rebleeding. Two meta-analyses (88,89) have come to identical results, i.e. that TIPS significantly reduces rebleeding as compared to endoscopic therapy (19% vs. 47%, $p < 0.001$), but significantly increases encephalopathy (34% vs. 19%, $p < 0.001$), while there is no difference in survival. Recently, two cost-effectiveness analyses comparing TIPS and endoscopic therapy have been made (90, 91). The first one (90), based on true patients data, shows that TIPS is not cost-saving in comparison with sclerotherapy ; the second one, (91) based on theoretical scenarios, suggests that TIPS may be cost-effective compared to endoscopic therapy in the short term. At any rate, TIPS is not considered a first-line therapy to prevent rebleeding (12) ; conceivably, TIPS can be viewed as a salvage treatment in patients who continue to rebleed despite pharmacologic or endoscopic treatment. In this setting, small diameter H-graft portacaval shunt could also be considered for patients who are good surgical risks. For patients with advanced cirrhosis, the feasibility of liver transplantation should also be considered (18).

In conclusion, all patients surviving an episode of variceal bleeding should enter a therapeutic program to prevent rebleeding. Beta blockers (with or without nitrates) and endoscopic band ligation (with or without beta-blockers) are the first-line treatment options.

Patients who continue to rebleed should be treated with TIPS. Depending on local resources, in good surgical risks, a small-diameter H-graft portacaval shunt can also been done, while poor risk patients should be considered for liver transplantation (18). Figure 6 shows an algorithm for prevention of variceal rebleeding.

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