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Current management of portal hypertension

Jaime Bosch[1,*], Juan G. Abraldes[1], Roberto Groszmann[2]

[1]*Hepatic Hemodynamic Laboratory, Liver Unit, IMD, Hospital Clinic, IDIBAPS, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain*
[2]*Hepatic Hemodynamic Laboratory, VA Medical Center, West Haven and Yale University School of Medicine, New Haven, CT, USA*

1. Natural History of portal hypertension and variceal bleeding

The management of portal hypertension should be based on an updated knowledge of its natural history. Portal hypertension is an almost unavoidable complication of cirrhosis, and it is responsible for the more lethal complications of this syndrome: gastro-esophageal varices and massive gastrointestinal bleeding, ascites, hepatorenal syndrome, and hepatic encephalopathy. Appearance of these complications represents the major cause of death and liver transplantation in patients with cirrhosis. The prevalence of esophageal varices is very high: when cirrhosis is diagnosed, varices are present in about 40% of compensated patients and in 60% of those with ascites [1,2]. After initial diagnosis of cirrhosis, the expected incidence of newly developed varices is about 5% per year [3]. Once developed, varices increase in size from small to large at an overall rate of 10–15% per year [3]. Progression of liver failure seems to be the factor with the greatest influence on overall growth [4]. On the other side, improvement in liver function and abstinence from alcohol may result in decrease or even disappearance of varices [5].

Once diagnosed, the overall incidence of variceal bleeding is to the order of 25% at 2 years in non-selected patients [6]. Many efforts have been made to define risk criteria for the development of variceal bleeding. The most important predictive factors related to the risk of bleeding are variceal size,-presence of red weal marks in the varices, and severity of liver dysfunction expressed by the Child–Pugh classification. These risk indicators have been combined in the north Italian endoscopic club (NIEC) index [7] which allows to classify patients into different groups with predicted 1-year bleeding risk ranging from 6 to 76%. However, the predictive power of this index is far from satisfactory. In a recent report, variceal size was found to be the best predictor of variceal bleeding, and this is the variable used to decide whether a patient should be given prophylactic therapy or not. The risk of variceal bleeding is about 7% at 2 years in patients with small varices (less than 5 mm), and increases to 30% at 2 years in patients with large varices [6]. Variceal size and red color signs are associated with increased bleeding risk probably because they contribute to marked increase in the tension of the wall of the varices, the decisive factor determining variceal rupture [8]. According to Frank's modification of Laplace's law, variceal wall tension is directly proportional to the transmural variceal pressure (the gradient between intravariceal and esophageal luminal pressures) and the radius of the varix, and inversely proportional to the thickness of the variceal wall. While variceal size is a function of variceal radius, red weal marks may represent areas of reduced wall thickness. Hepatic venous pressure gradient (HVPG) may constitute a good surrogate marker of transmural variceal pressure [9]. Indeed, cross-sectional and longitudinal studies demonstrated that variceal bleeding does not occur if HVPG remains below 12 mmHg [5,9–12].

It has been reported that 30–50% of cirrhotic patients with an acute variceal bleeding episode will die within 6 weeks [2], but it is likely that this figure overestimates the current mortality from variceal bleeding [13]. A more accurate, current figure may be a mortality of 20% at 6 weeks. Immediate mortality from uncontrolled bleeding is in the range of 5–8% [2,6].

Active bleeding at endoscopy [14], bacterial infection [15] and HVPG >20 mmHg measured early after admission [16] are significant prognostic indicators of failure to control bleeding. It is important to emphasize that variceal bleeding ceases spontaneously in 40–50% of patients. This is probably influenced by the fact that hypovolemia leads to reflex splanchnic vasoconstriction with reduced portal pressure and blood flow, a beneficial response that is nullified by blood transfusion [17,18].

The incidence of early rebleeding ranges between 30 and 40% within the first 6 weeks [6]. The risk peaks in the first 5 days with 40% of all rebleeding episodes occurring in this very early period [19]. Bleeding gastric varices, active bleeding at emergency endoscopy, low serum albumin levels, renal failure

* Corresponding author. Tel.: +34-93-227-54-00, ext. 5790; fax: +34-93-451-52-72.
E-mail address: jbosch@medicina.ub.es (J. Bosch).

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and HVPG >20 mmHg have been reported as significant indicators of early rebleeding risk [6]. Early rebleeding [14,19]and renal failure [20] are probably the most important prognostic factors for 6-week mortality, suggesting that their prevention should be a primary objective in the therapeutic approach to variceal bleeding.

Patients surviving a first episode of variceal bleeding have a very high risk of rebleeding and death. Median rebleeding incidence within 1–2 years in untreated controls of randomized controlled trials (RCTs) of non-surgical treatment for prevention of recurrent bleeding reported after 1981 is 63%. The corresponding mortality figure is 33% [2]. Because of these high risks, all patients surviving a variceal bleeding should be treated for prevention of rebleeding independently of other risk indicators [3,21]. Risk indicators of rebleeding and death are variceal size, Child–Pugh class, continued alcohol abuse and hepatocellular carcinoma [2].

2. Rationale for therapy

A very important concept which has been strongly substantiated in recent years is that the major factor determining the development of the complications and the clinical significance of portal hypertension is that portal pressure increases above a critical threshold value. HVPG [22], which accurately reflects portal pressure in the majority of liver diseases [23,24], is the most commonly used method to assess portal pressure in clinical practice. Varices do not develop until the HVPG increases to 10–12 mmHg, and the HVPG should be of at least 12 mmHg for the appearance of other complications, such as variceal bleeding and ascites [10,25,26]. Implicit in this concept is that preventing the HVPG to increase above these values will prevent the development of the complications of portal hypertension. The question that follows is if by reducing the HVPG below these thresholds, could complications of portal hypertension be prevented. Indeed longitudinal studies have demonstrated that if HVPG decreases below 12 mmHg by means of pharmacological treatment [11,12] or spontaneously due to an improvement in liver disease [5], variceal bleeding is totally prevented and varices may decrease in size. Besides, if this target is not achieved, a substantial decrease in portal pressure from baseline levels offers an almost total protection from variceal bleeding. This 'substantial' decrease in baseline HVPG needed to achieve protection was found to be of at least 20% [12], a finding confirmed in a number of subsequent studies [9,27–29]. This reduction in the HVPG of more than 20% and or a reduction below 12 mmHg are now accepted as the therapeutic targets in the treatment of portal hypertension. Moreover, the achievement of these targets may be associated with a lower risk of developing ascites [29,30], spontaneous bacterial peritonitis [30], hepatorenal syndrome [30] and death in the follow-up [29,30], thus demonstrating the reversibility of the portal hypertensive syndrome by means of pharmacological therapy. These findings provide the rationale for treatments aimed to reduce portal pressure.

Over the past decade, a better knowledge of the pathophysiology of portal hypertension and of the mechanism of variceal bleeding have provided the rationale for developing new agents capable of decreasing portal pressure. Unfortunately, only some of these new agents have been tested in clinical trials, which makes drug therapy in portal hypertension not much different today than it was 10 years ago.

Experimental studies have shown that the initial factor in the pathophysiology of portal hypertension is the increase in vascular resistance to portal blood flow. In cirrhosis this increase in resistance occurs at the hepatic microcirculation (sinusoidal portal hypertension). It is important to emphasize that, contrary to what was traditionally thought, increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder caused by the liver disease, but there is also a dynamic component, due to the active contraction of portal/septal myofibroblasts, activated stellate cells and portal venules [31–33]. This increase in the intrahepatic vascular tone is modulated by the increased activity of endogenous vasoconstrictors such as endothelin, alpha-adrenergic stimulus, leukotrienes, thromboxane A_2, angiotensin II and others [33–36], and is lessened by nitric oxide (NO), prostacyclin and by many vasodilating drugs (organic nitrates, adrenolytic agents, and calcium channel blockers) [37–39]. It is believed that in cirrhosis the hepatic vascular resistance is increased because of an imbalance between vasodilatory and vasoconstrictor stimuli, the former being insufficient to counteract the influence of the latter [31]. Indeed, in cirrhosis there is an increased activity of the abovementioned vasoconstrictors, while intrahepatic NO production is clearly decreased [31,40,41]. This deficient intrahepatic NO production is the result of an endothelial dysfunction in the liver microvascultature [40,41], and could have significance beyond the increase in vascular tone by promoting local thrombosis and fibrogenesis [31]. This has practical importance because it provides a rational basis for using NO-based therapies and other vasodilators in the treatment of portal hypertension. Another way of overcoming the increased resistance through the cirrhotic liver is by means of portal-systemic shunt surgery and transjugular intrahepatic portalsystemic shunts (TIPS). These procedures are highly effective in decreasing portal pressure, but have the detrimental effect that, by further decreasing portal blood flow through the liver and by increasing portal-systemic shunting, may enhance liver failure and facilitate hepatic encephalopathy.

A second and major contributing factor to portal hypertension is an increase in blood flow through the portal venous system, due to splanchnic arteriolar vasodilatation, which is caused by an excessive release of endogenous vasodilators (endothelial, neural and humoral) [42–46]. This contributes to aggravate the increase in portal pressure

and explains why portal hypertension persists despite the establishment of an extensive network of portosystemic collaterals that may divert over 80% of the portal blood flow. The increased portal venous inflow can be corrected pharmacologically by means of splanchnic vasoconstrictors such as vasopressin and its derivatives, somatostatin and its analogues and non-selective beta-adrenergic blockers, which are the drugs that have been more widely used in the treatment of portal hypertension. It should be theoretically possible to modulate splanchnic blood flow by acting on the mechanism responsible for the vasodilatation; however, this approach faces the difficulty of acting selectively on the splanchnic circulation

Splanchnic vasodilatation is accompanied by systemic vasodilatation, increased cardiac index and hypervolemia, representing the hyperkynetic circulatory syndrome associated with portal hypertension [47,48]. An expanded blood volume is necessary to maintain the hyperdynamic circulation, which provides a rationale for the use of low-sodium diet and spironolactone to attenuate the hyperkinetic syndrome and the portal pressure elevation in patients with cirrhosis [49].

Combined pharmacological therapy attempts to enhance the reduction of portal pressure by associating vasoconstrictive drugs, which act by decreasing portal blood inflow, and vasodilators, which reduce the intrahepatic vascular resistance [50].

Endoscopic therapy completes the spectrum of treatments for portal hypertension. These treatments are directed at 'eradicating' the varices by means of either injecting a variety of irritating substances into or around the varices to promote thrombosis and fibrosis, or by ligating the varices using elastic bands. These treatments do not decrease portal pressure and therefore have no effect on other complications of this syndrome. Moreover, it is possible that the efficacy of endoscopic therapy can be enhanced if combined with an agent that effectively lowers portal pressure. However, it is very likely that if the decrease in portal pressure gradient is clinically significant (i.e. greater than 20% of baseline or lower than 12 mmHg) there is no need for associating any invasive endoscopic procedures.

3. Current recommended therapy

The treatment of portal hypertension includes the prevention of variceal hemorrhage in patients who have never bled, the treatment of the acute bleeding episode and the prevention of rebleeding in patients who have survived a bleeding episode from esophageal or gastric varices. An additional scenario may come into practice: the 'pre-primary' prophylaxis, or treatment of compensated patients without varices in order to prevent the development of varices and ascites. The main difference among these scenarios is that natural history and prognosis are quite different from one to another. Knowledge of the natural history of each of these situations should guide the selection of therapies, since the hemostatic or prophylactic efficacy of the available treatments are directly proportional to their invasiveness and adverse effects.

3.1. Prevention of first bleeding and rebleeding

The modern era of drug therapy for portal hypertension started in 1980 with the publication by Lebrec et al. of the use of propranolol for prevention of recurrent variceal bleeding [51].

Since then, the efficacy of non-selective beta-adrenergic blockers has been assessed in a number of randomized controlled trials which consistently showed a significant reduction of the bleeding risk, both in the prophylaxis of first bleeding and in the prevention of rebleeding.

3.1.1. Prevention of first bleeding

(Table 1) A total of 12 trials assessing beta-adrenergic blockers for the prevention of first bleeding have been reported. Meta-analysis of these studies shows that continued propranolol or nadolol therapy reduces markedly the bleeding risk, from 25% with non-active treatment to 15% with beta-adrenergic blockers over a median follow-up of 2 years [3]. Mortality was only slightly reduced from 27 to 23%; this effect barely approached the level of statistical significance. The benefit of therapy has been proved in patients with moderate/large varices (>5 mm), either with or without ascites or with good or poor liver function [3,52]. There is no evidence at the moment to support treatment of patients with small varices [53]. Therapy with beta-adrenergic blockers should be maintained indefinitely, because when these are withdrawn the risk of variceal hemorrhage returns to what would be expected in an untreated population [54]. Moreover, it seems that patients who discontinue beta-adrenergic blockers experience increased mortality compared with an untreated population [54].

About 15–20% of patients are excluded from therapy with beta-adrenergic blockers in clinical practice because of relative or absolute contraindications [3,55]. In this subset of patients, treatment with isosorbide mononitrate (ISMN), despite its portal pressure lowering effect, is inef-

Table 1
Prophylaxis of first variceal bleeding: recommendations

- Patients without varices should be screened endoscopically for the appearance of varices every 2–3 years.
- Patients with small varices should be screened for enlargement of varices every 1–2 years. At present, there is no evidence to recommend treatment for prevention of variceal bleeding in these patients.
- Patients with medium or large varices should be treated with a non-selective beta-blocker if there are no contraindications. Available evidence does not support the use of combination therapy with non-selective beta-blockers and isosorbide mononitrate.
- Patients with medium or large varices with contraindications to or who can not tolerate beta-blockers should be considered for endoscopic banding ligation of varices. Isosorbide mononitrate alone is not a good treatment option for these patients.
- Treatment should be maintained indefinitely.

fective [55]. Variceal banding ligation is the only effective alternative for primary prophylaxis, but its use should be restricted to patients with large varices and intolerance or contraindications to beta-adrenergic blockers [56,57].

Because beta-adrenergic blockers are effective for the prevention of variceal bleeding, all patients with cirrhosis should be screened for the presence of esophageal varices at the moment of the first diagnosis of cirrhosis [53]. Some studies indicate that non-invasive tests (low platelet count, dilated portal vein and/or enlarged spleen at abdominal ultrasound) correlate with a high risk for varices, but so far none of these findings have proved accurate enough to avoid endoscopy [1]. In patients without varices on initial endoscopy, a second (follow-up) evaluation should be performed after 2–3 years [53]. Patients with small varices on initial endoscopy should have a follow-up endoscopy after 1–2 years to detect the progression of small to large varices [53].

3.1.2. Prevention of recurrent bleeding from esophageal varices

(Table 2) Because of the extremely high risk of rebleeding in untreated patients, all patients surviving a variceal bleeding should receive urgent and active treatment for the prevention of rebleeding [21,53,58]. In addition, those with poor liver function or with other recurrent complications of portal hypertension should be considered for liver transplantation.

3.1.2.1. First-line treatments. Either pharmacological treatment with beta-adrenergic blockers or endoscopic band ligation are accepted first-line treatments to prevent rebleeding. Pharmacological treatment has been based on the use of non-selective beta-adrenergic blockers [59]. Meta-analyses of these studies consistently found a marked benefit from beta-adrenergic blockers, both in terms of rebleeding (from 63% in controls to 42% in those under beta-adrenergic blockers) and mortality (from 27 to 20%) [3]. In the past recent years, beta-adrenergic blockers have been frequently given in association with ISMN, since this enhances the reduction in HVPG and increases the number of patients with a fall in HVPG of at least 20% [60–62]. Endoscopic injection sclerotherapy of esophageal varices also reduces both rebleeding and death [63]. Endoscopic band ligation has been proven superior to sclerotherapy in terms of efficacy and safety [63,64], and should be preferred to sclerotherapy [53]. A question arises as to whether pharmacological treatment should be preferred over banding ligation. This decision is obvious when there are contraindications to beta-adrenergic blockers. When there are none, no clear recommendations can be given, since in the three trials comparing these treatments (all using the combination of nadolol and ISMN in the pharmacological arm), drug therapy showed better [29], equal [65] or worse [66] results than band ligation. However, none of these trials showed a difference in survival between the two treatments. Patient preferences and local resources must be taken into account when making the choice [67].

With these therapies, rebleeding rate is still high, in the order of 30–50% at 2 years. More aggressive therapies such as surgical shunts or TIPS, though being more effective in preventing rebleeding [68,69], are not currently recommended as first-line treatments on the basis of their side effects. The combination of pharmacological therapy with endoscopic therapy as initial treatment may improve the results of either therapy alone [3,70], but available information is scarce and in most cases sclerotherapy has been the endoscopic therapy. Only one study compared the combination of band ligation plus beta-adrenergic blockers and sucralfate vs. ligation alone [71], suggesting better results in the combination group. This approach is particularly recommended in patients who rebleed despite either treatment alone. The association of beta-blockers and endoscopic therapy (preferably band ligation) is advisable in patients who bled under beta-blockers or under endoscopic therapy [3].

3.1.2.2. Second line treatments. Patients experiencing a significant episode of rebleeding while treated with beta-adrenergic blockers ± ISMN or endoscopic therapy should be considered for 'rescue' derivative therapies. Both TIPS and surgical shunts are very effective in preventing rebleeding [58,72], but surgical shunts, preferably an H-graft or a distal splenorenal shunt, should only be offered to patients with good liver function (Child A class) in centers with qualified surgeons.

3.2. Treatment of acute bleeding from esophageal varices

Variceal bleeding is a medical emergency and its management should be undertaken in an intensive care setting by a team of experienced medical staff, including well-trained nurses, clinical hepatologists, endoscopists and surgeons. The initial therapy is aimed at correcting hypovolemic shock, preventing complications associated with gastrointestinal bleeding, and achieving hemostasis at the bleeding site. The first two goals, which are independent of the cause of the hemorrhage, demand immediate management. Specific therapy to stop bleeding is usually given when the patient has had the initial resuscitation and following diagnostic endoscopy,

Table 2
Recommendations for prevention of variceal rebleeding

- Patients surviving a bleeding episode should be treated. Either non-selective beta-blockers or endoscopic band ligation can be used.
- Whenever possible, the hemodynamic effect of beta-blockers should be monitored. If a reduction of HVPG >20% or below 12 mmHg is not achieved, Isosorbide mononitrate may be added.
- The association of beta-blockers and endoscopic therapy (preferably band ligation) is advisable in patients bleeding under beta-blocker or endoscopic therapy.
- Patients with severe or repeat rebleeding while treated with beta-blockers associated with endoscopic therapy should be considered for 'rescue' therapy with TIPS (or shunt surgery in Child A patients).

Table 3
Treatment of acute variceal bleeding: recommendations

- The best approach is the combined use of a pharmacological agent, started from admission (or even during transferral to hospital) and an endoscopic procedure.
- Terlipressin, somatostatin, octreotide and vasopressin + nitroglycerin may be used (The order of preference is highly dependent on availability. When available, terlipressin and somatostatin are preferable). Drug therapy should be maintained at least for 48 h; 5-day therapy is recommended to prevent early rebleeding.
- Endoscopic band ligation or injection sclerotherapy are the endoscopic treatments of choice in bleeding esophageal varices. In bleeding gastric varices, endoscopic obturation with cyanoacrylate is preferable.
- TIPS should be used as a rescue procedure when medical and endoscopic therapy fails. Patients bleeding from gastric varices may require an earlier decision for TIPS.
- Shunt surgery using interposition mesocaval graft shunts or traditional portacaval shunts may be an alternative to TIPS in Child A patients.
- Blood volume restitution should be done cautiously, using packed red cells to maintain the hematocrit between 25–30%, and plasma expanders to maintain hemodynamic stability.
- Prophylaxis of infection with broad spectrum antibiotics should be given to all patients

with the important exception of pharmacological therapy, that can be started earlier in the course of the bleeding episode.

Blood volume replacement should be initiated as soon as possible aiming at maintaining the hematocrit between 25–30%. The avoidance of prolonged hypovolemia is particularly important to prevent complications such as infection and renal failure, which are associated with a high risk of rebleeding and death [6,20]. Over-transfusion should be avoided, not only because of the risks inherent with blood transfusion, but also because there may be a rebound increase in portal pressure with a subsequent risk of continued bleeding or rebleeding [73,74]. Antibiotic prophylaxis should be instituted from admission and the presence of infection should be investigated. Antibiotics, together with terlipressin, are the only drugs proven to improve survival in the acute variceal bleeding episode [75]. Norfloxacin, 400 mg/12 h, is the first choice antibiotic prophylaxis due to its simpler administration and lower cost [76].

The current recommended hemostatic treatment of variceal bleeding is to start a vasoactive drug from admission, and associate endoscopic therapy at the time of diagnostic endoscopy (Table 3) [53,77]. Drug therapy may actually be started upon the patient's transfer to the hospital by medical or paramedical teams [78] and maintained for up to 5 days to prevent early rebleeding [53]. With this approach, initial control of bleeding is obtained in about 75% of patients. The rationale for this combined treatment comes from a number of randomized controlled trials demonstrating that early administration of vasoactive drugs facilitates endoscopy, improves control of bleeding and reduces 5-day rebleeding rate [78–80]. Drug therapy still improves the results of endoscopic treatment even if started just after sclerotherapy or band ligation [3,81,82]. Besides, it seems that the association of endoscopic therapy improves the efficacy of vasoactive treatment alone, both in low-risk and high-risk patients [83]. However, as in most trials in acute variceal bleeding, this combined approach failed to improve 6-week mortality with respect to endoscopic therapy [84] or a vasoactive drug alone [83]. On the other hand, vasoactive therapy with a single agent is as effective as endoscopic therapy, but with significantly less side effects [85], which questions the use of endoscopic therapy as single treatment.

The selection of the drug depends on the local resources. Terlipressin should be the first choice, if available, since it is the only drug that has been shown to improve survival [78]. Somatostatin, octreotide or vapreotide are the second choice [3,82]. If these drugs are not available, vasopressin plus transdermal nitroglycerin is an acceptable option [3]. Regarding endoscopic therapy, in the acute bleeding episode either sclerotherapy or band ligation may be used [70], the former avoiding repeated intubation.

3.2.1. Rescue therapies

In the face of early recurrent bleeding, the attendant physician must weigh it's severity . A single endoscopic retreatment may be offered if bleeding is mild and does not compromise the patient. If this is not so, a derivative treatment should be offered. Balloon tamponade can be used as a temporal 'bridge' until definite treatment is performed in case of a massive bleeding.

Both TIPS and surgical shunts are extremely effective in the control of variceal bleeding (control rate approaches 95%), but their invasiveness and post-procedure complications (mainly encephalopathy and worsening liver function) result in a high mortality [58,72,86]. TIPS is the first choice, since most patients have advanced liver disease [87]. Shunt surgery, preferably a H-graft meso-caval shunt, may be an alternative in Child A patients if an experienced surgeon is available.

4. Problems in management

4.1. Drug therapy: beta-adrenergic blockers, nitrates and their combination

Non-selective beta-adrenergic blockers are the most widely used drugs to treat portal hypertension. However, only 30–40% of the patients under long-term therapy reduce their portal pressure $\geq$20% from baseline or to levels $\leq$12 mmHg [12]. Lack of achievement of these hemodynamic targets constitutes the strongest independent predictor of variceal bleeding or rebleeding [12,27], indicating that the available armamentarium to treat portal hypertension is far from optimal.

The first question is the choice of beta-blocker. This should be non-selective, i.e. blocking both beta-1 cardiac receptors and beta-2 vascular receptors. However, there

appears to be no difference in the efficacy of propranolol and nadolol, the only non-selective beta-adrenergic blockers tested in clinical trials [3]. In the authors' experience, intolerance to one may be overcome by shifting to the other. Nadolol may be more convenient since it can be administered once a day, and due to its low-lipid solubility it may have a lower potential for central side effects [88]. Timolol also has low liposolubility [88], and has the greatest beta-2 adrenoceptor blocking effect [89], which may increase portal pressure response [90]. It is being tested in a large ongoing randomized trial.

The second question is how to adjust the dose to maximize the beneficial effects of beta-adrenergic blockers. Currently, the dose of beta-adrenergic blockers is determined by stepwise increases in dose until the heart rate decreases by 25% or below 55 beats/min, or the appearance of arterial hypotension or intolerance [50]. This means that these drugs are titrated against the degree of beta-1-adrenoceptor blockade (reflected by the decrease in heart rate), and clinical tolerance. However, the beneficial effects of beta-adrenergic blockers in portal hypertension are due to blockade of both beta-1 and beta-2 adrenoceptors [90,91], and the degree of beta-1 blockade does not correlate with the fall in portal pressure [92,93]. Besides, old data suggest that some 'non-responders' could be rescued just by increasing the dose of propranolol [93]. Thus, titration solely against clinical tolerance could add some advantage over what has been the standard practice. This approach has already been used in a clinical trial, but higher rate of side effects and withdrawals than in previous trials were recorded [94].

Another approach to increase the proportion of responders to propranolol has been the addition of a vasodilating drug. The rationale underlying this approach is that some patients do not respond to propranolol due to an increase in portocollateral (and maybe intrahepatic) resistance [95,96], hindering the reduction in portal pressure. Indeed, the addition of ISMN have been shown to significantly increase the long-term response to beta-adrenergic blockers [60,61] without adverse effects on renal function [97,98]. What has been extensively debated is whether the greater effect of this combination on portal pressure translates into a greater clinical efficacy. In primary prophylaxis, an open trial comparing nadolol vs. nadolol plus ISMN demonstrated a significant lower rate of first bleeding in the combination group, that was maintained after 55 months of follow-up, without survival advantage [99,100]. However, two subsequent double-blind, placebo controlled studies not yet published in full [101,102], one of them including a large number of patients [102], failed to confirm these results. Current consensus cannot recommend the use of combination therapy in primary prophylaxis [53]. In prevention of rebleeding, two trials are available [103,104], one of them double blind and placebo-controlled, but only available in abstract form [103]. These studies failed to show a benefit from combination therapy in terms of rebleeding or survival. Thus, although beta-adrenergic blockers plus nitrates combination therapy has been recommended on the basis of its superiority over sclerotherapy or band ligation [28,29] it has not proven to be better than beta-adrenergic blockers alone. We recommend the evaluation, whenever possible, of the hemodynamic response to beta-adrenergic blockers. If a decrease in HVPG of $\geqslant 20\%$ or to ≤ 12 mmHg is not achieved with beta-blockers alone, ISMN may be added. Actually, such 'a la carte' treatment approach has been supported by the results of a recent study [62].

The newest approach to increase response to beta-adrenergic blockers has been the use of carvedilol. This drug combines a non-selective beta-blocker action with an alpha-1-adrenoceptor blocking activity and, thus, mimics the effects of the combination therapy of propranolol/nadolol plus prazosin, which causes a very pronounced decrease in portal pressure but is associated with excessive hypotension [105]. In a recent study, the acute administration of carvedilol induced a marked decrease in portal pressure gradient that was significantly greater than that achieved by propranolol, despite causing similar reductions in splanchnic blood flow [106]. This suggests that carvedilol did decrease hepatic and/or portocollateral resistance due to its anti-alpha1-adrenergic activity. However, studies evaluating its long-term effect showed discrepant results. In one study, a 25 mg/day dose of carvedilol was associated with marked hypotension leading to discontinuation of the treatment in a significant proportion of patients [107]. Subsequent studies showed that lower doses (12.5 mg/day) [108] or careful titration [109] result in good tolerance, maintaining the portal hypotensive effect [108,109]. Indeed, when compared with propranolol in a randomized trial [109], carvedilol significantly increased the number of patients (54 vs. 23%) achieving a target reduction in HVPG (of $\geq 20\%$ from baseline or below 12 mmHg). This drug should be further evaluated in randomized trials with clinical end-points.

4.2. HVPG monitoring

Measurement of the HVPG is an indirect method of assessing portal pressure. The procedure is performed under local anesthesia (at puncture site) and is very safe. To optimize the measurement, avoid underestimation and increase reproducibility it should be performed with a balloon catheter [22].The authors have not had any lethal complications in over 10,000 studies. Conscious sedation with low dose midazolam (0.02 mg/kg) increases patient comfort and willingness to undergo repeated procedures, without modifying hepatic pressures [110]. Specific training is required to obtain accurate measurements, since the procedure differs from that used at heart catheterization labs and intensive care units (ICUs).

It is becoming increasingly clear that repeated HVPG measurements provide important prognostic information in patients with cirrhosis, especially during continued drug therapy [5,9,11,12,27–29,62]. So far no other test/procedure has been as reliable. HVPG response correlates with morbidity and mortality from portal hypertension. Also,

repeated HVPG measurements can be used to guide therapy, much like serial blood pressure measurements are used in the guidance of antihypertensive therapy. Unfortunately, objective benefits obtained from tailoring therapy against hemodynamic response are still not well defined, mainly due to the scarcity of specific studies.

Assessing HVPG response to drug therapy may not be cost effective in primary prophylaxis due to the low rate of bleeding and the overall good protection afforded by medical therapy. However, in a high bleeding risk situation, such as is faced by patients who have already bled from varices, HVPG monitoring provides extremely useful prognostic information and should be recommended.

The still unsolved but key question is what to do with patients who do not achieve a good hemodynamic response with drug therapy. This approach has only been evaluated very recently [62], and showed that patients not achieving a decrease in HVPG of $\geq$20% or to $\leq$12 mmHg had a very high risk of rebleeding, despite endoscopic band ligation 'rescue therapy'. This means that prognosis of 'non-responders' may not necessarily be improved by adding endoscopic therapy, and that these patients may require more aggressive treatments, such as TIPS or liver transplantation. On the other hand, new RCT's for prevention of variceal bleeding should take into account that prognosis in responders is so favorable that it may not be improved by any new therapy.

4.3. Primary prophylaxis with band ligation

When comparing band ligation with no treatment, a marked and significant reduction of both bleeding and death risk is observed [56]. A recent meta-analysis by Imperiale et al. suggested that endoscopic variceal band ligation would be better than beta-adrenergic blockers in preventing the first variceal bleeding [56]. This raised the question of whether this therapy should be the first option for primary prophylaxis. That meta-analysis included four trials [94,111–113], only two of them reported in full [112,113]. Since then, one of the trials was published in full [94] and one more abstract became available [114]. The meta-analysis of these five trials, including a total of 346 patients, shows no significant differences between endoscopic band ligation and beta-adrenergic blockers either for bleeding or death (D'Amico, personal communication). Only one study showed a significant benefit with ligation [113]. However, the bleeding rate in patients given propranolol was unusually high, similar to that reported by the same group with no therapy [115]. Therefore there is no evidence to support that endoscopic band ligation is superior to beta-adrenergic blockers, and there is no rationale for the use of band ligation as first-line prophylactic therapy, since the advantages of beta-blocker therapy in terms of cost and convenience for the patient are obvious. Also, band ligation does not act by reducing portal pressure, which could reduce the risk of developing other complications of portal hypertension [29,30]. Band ligation, however, is a good (and currently the only) option for patients with high-risk varices and contraindications to beta-adrenergic blockers.

Preliminary results of an ongoing trial suggest that the combination of propranolol with endoscopic variceal ligation (EVL) is not superior to EVL in terms of preventing the first bleeding, but may reduce the incidence of variceal recurrence [116]. This combination should be tested in the future against beta-adrenergic blockers $\pm$ISMN.

4.4. Problems in the acute bleeding patient: duration of drug therapy, best moment for endoscopic therapy

4.4.1. Duration of drug therapy

While there is consensus in that a vasoactive drug should be started from admission, or prior to admission by paramedicals during transfer of the patient to the hospital, the optimal duration of drug therapy is not well established and requires evaluation. Current recommendation is to maintain the drug for 5 days. The rationale for this would be to cover the period of maximum risk of rebleeding. However, the magnitude of the reduction on portal pressure achieved by continuous infusions of somatostatin is mild, and is almost nil when using octreotide [82]. It is possible that the beneficial effects of these drugs could be other than a portal pressure hypotensive effect, such as preventing the increases in HVPG induced by the presence of blood in the gastrointestinal tract or by volume restitution. Such increases in HVPG may favour hemorrhage persistence or recurrence [17,18,13,117]. This has been already shown for somatostatin [118]. Terlipressin has also been shown to achieve a low 5-day rebleeding risk. However, in the trial by Levacher et al. [78] survival was improved in terlipressin plus endoscopic treatment group even though it was only administered for 12 h.

4.4.2. Best moment for endoscopic treatment

Probably, endoscopic therapy should be performed at the time of diagnostic endoscopy, early after admission (within 12 h). However, if there is no active bleeding and the patient is stable, endoscopic treatment can probably be postponed until normal working hours. This approach allows endoscopic therapy to be performed in the best conditions by skilled endoscopist and an experienced nursing team, instead of the commonly less skilled physicians on duty. This may reduce the complication and the burden from emergency endoscopic procedures.

4.5. The problem of gastric varices and portal hypertensive gastropathy

4.5.1. Gastric varices

Gastric varices are the source of 5–10% of all upper digestive bleeding episodes in patients with cirrhosis. The treatment of gastric varices has seldom been evaluated in randomized trials and most available information comes from retrospective series and case reports. The better knowledge gained on

the natural history and the availability of a useful prognostic classification of gastric varices [119] should enhance new large-scale multi-center randomized trials for this condition.

The risk of first bleeding from gastric varices is no greater than that from esophageal varices. It is conceivable that pharmacological therapy is equally effective in this situation. Therefore, non-selective beta adrenergic blockers should be given to these patients to prevent the first bleeding episode.

The optimal treatment of acute gastric variceal bleeding is not known. The usual initial treatment is a vasoactive drug, either terlipressin, somatostatin or a somatostatin analogue, but this has not been evaluated in specific studies. Balloon tamponade, with the Linton–Nachlas tube, has been used with limited success [120,121], but may serve as a bridge to derivative treatments in massive bleedings.

Some endoscopic therapies are promising, but quality information is scarce. Sclerotherapy, glue injection, thrombin, elastic band ligation and ligation with large detachable snares have been reported [122]. In most uncontrolled series cyanoacrylate is highly effective, in the order of 90% [123–125]. A recent randomized controlled trial confirmed that endoscopic obturation using cyanoacrylate was more effective and safer than band ligation in the management of bleeding gastric varices [126]. Also, in another RCT by Sarin and coworkers, cyanoacrylate was better than alcohol injection in achieving initial hemostasis and in achieving faster variceal obliteration [127]. Novel endoscopic therapies are under evaluation. Among them, the use of human thrombin injection [128,129] seems the most promising, since it avoids mucosal damage and ulceration. These techniques need expertise, and may not be feasible when bleeding is massive.

TIPS is very effective in the treatment of bleeding gastric varices, with more than 90% success rate for initial hemostasis and low rebleeding rate [130,131]. In these patients many centers associate TIPS with the embolization of the collateral vessels that feed the varices. Derivative and devascularization surgery are also effective [122], but with limited applicability in advanced cirrhosis.

The authors recommendation is to start with a vasoactive drug. If bleeding is not controlled, and an expert endoscopist is available, endoscopic treatment (cyanoacrylate or human thrombin) should be attempted. In cases of massive bleeding or after failure of previous therapies, TIPS (or surgical shunt in Child A patients) is mandatory. In some cases TIPS may be used even before attempting further endoscopic therapy.

New trials comparing TIPS or surgery with pharmacological and endoscopic therapy, both in acute bleeding and in prevention of rebleeding, are needed.

4.5.2. Portal hypertensive gastropathy

In the largest study on the natural history of portal hypertensive gastropathy (PHG), the overall prevalence of this condition in patients with cirrhosis was 80% [132]. Its prevalence is strongly correlated with the severity of portal hypertension. However, the incidence of bleeding is low: acute bleeding occurred in 2.5% of the patients over a 18 month follow-up, with a mortality of 12.5%, while the incidence of chronic bleeding was 12%.

Propranolol, somatostatin, octreotide, vasopressin, terlipressin and estrogens have been proposed for the treatment of PHG based on their ability to decrease gastric perfusion in this condition [133–136]. However, only one uncontrolled study so far has evaluated one of these drugs (somatostatin) in the treatment of acute bleeding from PHG [137], achieving hemostasis in all patients. Propranolol has been found to reduce recurrent bleeding from PHG in a randomized trial [138]. The role of derivative treatments is controversial. Reported results with shunt surgery and TIPS suggest that these treatments are effective [139–141], but due to the lack of randomized studies, the fluctuating nature of PHG and, possibly, unreported failures, both TIPS and shunt surgery should be considered only as rescue therapies for the uncommon patient who has repeated bleeding from PHG despite propranolol treatment. Liver transplantation reverses portal hypertension and therefore effectively treats PHG [142].

4.6. Problems with TIPS

TIPS is now widely used for the treatment of portal hypertension. It has been tested in randomized trials for the prevention of variceal rebleeding [72] and for the treatment of refractory ascites [143,144]. In many other situations TIPS is used based on 'good' results in small, uncontrolled studies, such as rescue therapy for uncontrolled acute variceal bleeding, recurrent variceal bleeding despite pharmacological and/or endoscopic therapy, bleeding gastric varices, hepatic hydrothorax and Budd–Chiari syndrome.

4.6.1. TIPS in uncontrolled bleeding, for all?

TIPS is quite effective as a salvage haemostatic therapy for uncontrolled variceal bleeding, and this probably constitutes its most accepted indication. The success rate in arresting bleeding is over 90%, but is burdened by a mortality that exceeds 30% [86,145]. These mortality figures approach 100% in patients with sepsis, inotropic support, ventilated after aspiration, and with deteriorating liver and renal function [72]. This clearly indicates that some patients do not benefit from TIPS in this setting, and most times it is not difficult to make a clinically based decision. Rarely, if ever, a patient with a Child–Pugh score over 13 will survive TIPS. Prognostic scores, such as that developed by Patch et al. [146], may provide objective parameters to facilitate the decision of not offering invasive treatments in some cases.

4.6.2. TIPS as first-line treatment, for some?

The field in which TIPS has been more extensively evaluated in randomized trials is in the secondary prophylaxis of variceal bleeding. A large corpus of consistent data indicates that it is more effective than endoscopic therapy in preventing rebleeding [68]. A single trial demonstrated that it is also better than pharmacological therapy with propranolol and ISMN

[69]. However, TIPS is associated with increased rate of encephalopathy, does not increase survival [68], and is more expensive than drug therapy [69]. TIPS, thus, should not be used as first-line treatment to prevent rebleeding.

4.6.3. Always TIPS, or some shunts?

Another problem with TIPS is whether it should be preferred to surgical shunts in patients with good liver function (Child A or 'good' B). Only one RCT has assessed this issue so far. This trial compared TIPS with a 8 mm prosthetic H-graft portocaval shunt, showing a lower rate of rebleeding, death and liver transplantation in the surgical group [147]. An ongoing large RCT comparing TIPS and distal splenorenal shunt will provide additional data [87]. In the meantime, if an experienced surgeon is available and the patient is unable to comply with the follow-up protocol of TIPS, a surgical shunt is the best option. If a liver transplantation is in perspective a properly placed TIPS seems to have the minimal deleterious effect [87].

4.6.4. TIPS dysfunction

The major advantage of surgical shunts as compared to TIPS is long-term patency, since over 50% of TIPS develop stenosis within 1 year [26,148]. This requires a regular program of shunt surveillance with ensuing reinterventions and high costs. Covered stents, such as the new polytetrafluoroethylene-covered stent-graft, seem to markedly improve patency figures [149], still their influence on encephalopathy, liver function and survival rates should be carefully evaluated before their widespread use. Another approach to overcome TIPS dysfunction is to associate drugs that decrease splanchnic blood flow. Two recent studies have demonstrated that propranolol [150] or octreotide [151] are able to decrease portal pressure gradient in patients with TIPS dysfunction.

5. New trends in drug therapy

5.1. New drugs to treat portal hypertension

5.1.1. Drugs that decrease hepatic resistance

Theoretically, in portal hypertension an ideal drug should act by decreasing intrahepatic vascular resistance, therefore decreasing portal pressure, while maintaining or enhancing hepatic blood flow. The vasodilatory effect of such a drug should be limited to the hepatic microcirculation to prevent a worsening in splanchnic/systemic vasodilatation. Furthermore, if such a drug were also capable of decreasing hepatic fibrosis and improving liver function, then many hepatologists would become unemployed. The development of such a drug is desperately desired, but far from reality.

5.1.1.1. Alpha-1 adrenergic blockers. Prazosin is an alpha-1 adrenergic antagonist that markedly reduces HVPG in patients with cirrhosis. This reduction is associated with an increased hepatic blood flow, suggesting a reduction in the hepatic vascular resistance [152,153]. However, chronic prazosin administration is associated with a significant reduction in arterial pressure and systemic vascular resistance and with an activation of endogenous vasoactive systems leading to plasma volume expansion, sodium retention and in some cases, to the accumulation of ascites [153]. These findings discouraged its use in the treatment of portal hypertension. The adverse effects of prazosin on the systemic circulation and renal function are attenuated by the combined administration of prazosin and propranolol. More interesting, the association of propranolol plus prazosin was significantly more effective, in terms of reducing HVPG, than the association of propranolol plus ISMN [105]. This drug combination has not been assessed in RCT's.

5.1.1.2. Renin-Angiotensin system blockers. Activation of the renin-angiotensin system is a frequent finding in patients with cirrhosis, especially in those with more advanced disease. Angiotensin II may act on hepatic circulation, increasing hepatic resistance and contributing to portal hypertension. Blockade of this system has been tested as another approach to treat portal hypertension. In a recent non-randomized study in patients with portal hypertension, losartan, a non-peptide antagonist of angiotensin-receptor type I, caused a dramatic reduction in portal pressure with only slight arterial hypotension and no significant adverse effects [154]. This impressive findings, however, were not confirmed in subsequent RCT's, in which Angiotensin-II blockade with irbesartan or losartan had slight or null effect on portal pressure, while decreased arterial pressure and GFR [155–157]. These agents are dangerous in advanced cirrhosis, but may still have a role in preventing the progression of hepatic fibrosis in early stages of the disease [158].

5.1.1.3. Endothelin receptor blockers. Endothelin also increases hepatic resistance in cirrhosis. However, conflicting results have been obtained with the use of endothelin blockers in experimental models of portal hypertension. Acute administration of the mixed ETA–ETB receptor blocker bosentan decreased portal pressure [159,160], while chronic administration of RO 48-5695, a second generation mixed ET-receptor blocker, did not modify portal pressure and even increased liver fibrosis [161]. On the contrary, chronic selective blockade of ETA receptor with LU 135252 dramatically decreased collagen accumulation in rats with secondary biliary cirrhosis [162], while acute administration of another ETA blocker (FR 139317) to cirrhotic rats did not lower portal pressure [163]. Obviously more research is needed in this area.

5.1.1.4. Selective hepatic delivery of NO. It is increasingly recognized that insufficient availability of NO in the hepatic circulation is implicated in the increase in hepatic vascular tone as well as in fibrogenesis [164] and local thrombotic

phenomena, that may contribute to the progression of cirrhosis [165]. This suggests that prolonged administration of orally active hepatic NO donors could modify not only the dynamic component of increased intrahepatic resistance, but also ameliorate fibrosis and delay the progression of cirrhosis. However, in patients with advanced cirrhosis the use of non-liver-selective NO donors, such as ISMN, enhances peripheral vasodilatation, further decreasing arterial blood pressure and activating endogenous vasoactive systems. So far, the administration of ISMN has proven clinically ineffective in terms of prevention of variceal bleeding [55,94,166,167].

Liver-specific NO donors are being investigated. These agents would be devoid of systemic vasodilatory effects, and thus will be close to the attributes of the ideal drug for the treatment of portal hypertension. In a preliminary report, a liver selective NO donor V-pyrro/NO, decreased portal pressure in a model of cirrhosis, without significant systemic effects [168], but the real selectivity of this drug is being questioned [31] (Groszmann, unpublished information). In another recent study, the continuous administration of NCX-1000, a NO-releasing derivative of ursodeoxycholic acid, prevented ascites formation and reduced hepatic resistance in cirrhotic rats [169]. There are no data on the effects of these two drugs on patients with cirrhosis.

Another experimental approach has been to enhance the expression of NO-synthase (NOS) in liver cells through the portal injection of adenovirus coupled with the gene encoding endothelial NOS [170,171] or neuronal NOS [172]. Enhancement of NOS expression was associated with a significant reduction in portal pressure in cirrhotic rats [170,173]. However, there is still a long way and many technical problems to solve before this gene-based therapy may be translated into clinical practice. On the other hand, if it would be possible to selectively deliver NO to the liver with drugs, it would seem unnecessary to deal with the complexities and risks of gene therapy.

5.1.2. Drugs that decrease splanchnic blood flow

The large amount of information gathered on the mechanism of splanchnic vasodilatation and increased portal inflow in cirrhosis [31,174] has not yet been of any therapeutic benefit for patients with portal hypertension. 'Old' drugs such as beta-adrenergic blockers, vasopressin and somatostatin and their respective derivatives still are the only vasoconstrictors used in clinical practice. Vasoconstrictors have other advantages in advanced cirrhosis, since they improve renal function and the hyperdynamic state [175–177]. These drugs, however, by decreasing portal inflow may impair liver function.

5.1.2.1. NO blockers. Available data on the effects of systemic NO blockade in patients with cirrhosis are still insufficient. A very recent report showed that systemic administration of the NOS inhibitor N^G-monomethyl-L-arginine (L-NMMA) to patients with cirrhosis and portal hypertension corrected systemic hemodynamics and improved renal function and sodium excretion [178]. However, as observed in the experimental setting [45] and in cirrhotic patients in a previous report with the same drug [179], the increase in hepatic resistance caused by NO inhibition may offset the reduction in portal inflow, resulting in no decrease in portal pressure. This is probably due to the fact that intrahepatic NO, although insufficient, still plays an important role in regulating hepatic vascular tone. Furthermore, hepatic NO production, even if reduced, may still be protective delaying the progression of cirrhosis. Therefore, new NO blockers without any hepatic effect would be required.

5.2. New prospects in the management of acute variceal bleeding

Further refinement in the use of currently available resources for the treatment of variceal bleeding is still possible. Somatostatin and octreotide doses used in clinical practice are clearly suboptimal from the hemodynamic point of view [82,180,181]. A recent RCT suggested that the use of higher doses (500 μg/h) of somatostatin can translate into increased clinical efficacy in the subset of patients with more severe hemorrhage (those with active bleeding at emergency endoscopy) [182]. Another recent study has shown that measurements of HVPG within 48 h of admission for acute variceal bleeding provide useful prognostic information on the outcome of the bleeding episode and long-term survival [16]. In that study, an initial HVPG of $\geq$ 20 mmHg was associated with a significantly greater risk of failure to control bleeding (23 vs. 0%), early rebleeding (50 vs. 12%), longer ICU stay, longer hospital stay, greater transfusion requirements, and a worse actuarial probability of survival (1-year mortality, 64 vs. 20%). If confirmed, such high risk patients might benefit from early aggressive therapy for instance with TIPS.

The influence of coagulopathy and thrombocytopenia in the outcome of acute variceal bleeding, and the use of replacement therapy (fresh frozen plasma, cryoprecipitates and platelets) has not been assessed in RCT's [53]. Recently, recombinant activated factor VII (rVIIa), has shown to correct prothrombin time in cirrhotics, both in non-bleeders [183], and in the acute variceal bleeding setting [184]. Ongoing trials are evaluating its possible utility in acute variceal bleeding.

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