Review

The management of portal hypertension: Rational basis, available treatments and future options[☆]

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Variceal bleeding is the last step in a chain of events initiated by an increase in portal pressure, followed by the development and progressive dilation of varices until these finally rupture and bleed. This sequence of events might be prevented – and reversed – by achieving a sufficient decrease in portal pressure. A different approach is the use of local endoscopic treatments at the varices. This article reviews the rationale for the management of patients with cirrhosis and portal hypertension, the current recommendations for the prevention and treatment of variceal bleeding, and outlines the unsolved issues and the perspectives for the future opened by new research developments.
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1. The syndrome

1.1. Definition

Portal hypertension is a common clinical syndrome, which is hemodynamically defined by a pathological

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    Abbreviations: CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; PVT, portal vein thrombosis; NO, nitric oxide; VEGF, vascular endothelial grow factor; PDGF, platelet derived grow factor; TIPS, transjugular intrahepatic porto-systemic shunt; MRI, magnetic resonance imaging; NASH, non-alcoholic steato-hepatitis; BB, beta-blockers; EBL, endoscopic band ligation; ISMN, isosorbide 5-mononitrate; RCT, randomised controlled trial; PHG, portal hypertensive gastropathy; RR, relative risk; OR, odds ratio; HR, hazard ratio.

increase of the portal pressure gradient (the pressure difference between the portal vein and the inferior vena cava) and by the formation of portal–systemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver [1]. Normal values of the portal pressure gradient are of 1–5 mm Hg.

Clinically significant portal hypertension (CSPH) is diagnosed when clinical manifestations of the disease appear or when portal pressure gradient – in case of cirrhosis determined by its equivalent, the hepatic venous pressure gradient (HVPG) [2] – exceeds a threshold value of 10 mm Hg. Values of portal pressure gradient between 5 and 9 mm Hg correspond to pre-clinical portal hypertension [3–6].

1.2. Aetiology and classification (Table 1)

Portal hypertension can arise from any condition interfering with blood flow at any level within the portal system. According to the anatomic location of the obstacle to blood flow the causes of portal hypertension can be classified as *prehepatic* (involving the splenic,

Table 1
Classification of portal hypertension according to the anatomic site of increased resistance to portal blood flow

Prehepatic
    Splenic vein thrombosis
    Portal vein thrombosis
    Congenital stenosis of the portal vein
    Extrinsic compression of the portal vein
    Arteriovenous fistulae

  Intrahepatic
    Cirrhosis (*viral, alcoholic, biliary, metabolic*)
    Granulomatous diseases (schistosomiasis, sarcoidosis,
      tuberculosis, PBC)
    Partial nodular transformation[*]
    Nodular regenerative hyperplasia[*]
    Congenital hepatic fibrosis
    Peliosis hepatis
    Polycystic disease[*]
    Idiopathic portal hypertension[*]
    Hypervitaminosis A
    Arsenic, copper sulfate, vinyl chloride monomer poisoning
    Amyloidosis
    Mastocytosis
    Rendu-Osler-Weber síndrome
    Liver infiltration in hematologic diseases
    Acute fatty liver of pregnancy
    Severe acute viral and alcoholic hepatitis
    Chronic active hepatitis
    Hepatocellular carcinoma
    Cyanamide toxicity
    Veno-occlusive disease

Posthepatic
    Hepatic vein thrombosis (Budd-Chiari syndrome)
    Congenital malformations and thrombosis of the inferior vena
      cava
    Constrictive pericarditis
    Tricuspid valve diseases

[*] Exhibit a "pre-sinusoidal" pattern.

mesenteric or portal vein), *intrahepatic* (liver diseases) and *posthepatic* (diseases blocking the hepatic venous outflow).

Cirrhosis of the liver determines about 90% of cases of portal hypertension in Western countries, while Schistosomiasis is the first cause in other countries. Other causes of portal hypertension account for less than 10% of cases worldwide, which explains why these are frequently referred to as *non-cirrhotic portal hypertension*.

The more frequent cause of *prehepatic* portal hypertension is portal vein thrombosis (PVT). In children this is often secondary to omphalitis, while in adults thrombophilic syndromes, either congenital (such as protein C and S deficiency) or acquired (such as latent myeloproliferative disease) in addition to local factors (such as sepsis, abdominal trauma or surgery) can explain the onset of thrombosis in up to 70% of cases [7]. In about 30% these factors are not identified ("idiopathic" PVT) [7]. Acute portal vein thrombosis is uncommon, usually manifested by abdominal pain and fever; in few cases with extended thrombosis, diarrhoea and ileus may

appear as a consequence of intestinal infarction. The diagnosis is usually made by imaging techniques. Chronic PVT is characterized by the formation of collateral vessels that "bridge" the obstruction, causing the appearance of the so-called portal "cavernoma". Patients with chronic PVT develop the same hemodynamic abnormalities as in other causes of portal hypertension, and are frequently diagnosed after a first episode of variceal bleeding. Gastric varices are a frequent finding in PVT: Treatment options include anticoagulation in the acute phase (which should be perpetual in patients with thrombophilic disorders), and medical and endoscopic therapy for portal hypertension complications in the chronic phase.

The more frequent cause of *posthepatic* portal hypertension is the Budd-Chiari syndrome (hepatic vein thrombosis). Obstruction can occur at the main hepatic veins or in suprahepatic inferior vena cava. Similarly to PVT, one or several underlying prothrombotic disorders are usually present, the most common of which is an overt or occult primary myeloproliferative disorder. Major complications are ascites and gastrointestinal bleeding associated with a variable degree of liver failure. The disease can present as an acute, subacute or chronic disease. Diagnosis is usually made by imaging techniques [8,9]. Treatment includes anticoagulation to prevent recurrence or extension of thrombosis, treatment of ascites and gastrointestinal bleeding, and procedures aiming at re-establishing hepatic blood outflow. Transjugular intrahepatic porto-systemic shunt (TIPS) has substituted derivative surgery in patients who do not improve with medical treatment. Transplantation is proposed for patients with severe liver failure [10,11].

Intrahepatic causes of portal hypertension have been classified according to the results of hepatic vein catheterisation. This classification includes:

(a) *pre-sinusoidal PH*: normal wedged and free hepatic venous pressure (WHVP and FHVP);
(b) *sinusoidal PH*: increased WHVP and normal FHVP;
(c) *post-sinusoidal PH*: increased WHVP and FHVP.

Some disorders may act at several sites; for example, in Schistosomiasis portal hypertension is the consequence of the formation of granulomas due to the deposition of parasite eggs in portal venules. The inflammatory response induces fibrosis and obliteration of portal venules (pre-sinusoidal PH), which later extends to sinusoids (sinusoidal PH). At this time the hemodynamic and clinical pattern resemble those of liver cirrhosis.

Any cause of chronic liver disease, except chronic cholestatic syndromes cause sinusoidal PH. Since cirrhosis is the leading cause of PH, the next sections of this article will focus on cirrhotic portal hypertension.

1.3. Clinical manifestations: a multiorgan disease

The relevance of the portal hypertensive syndrome is due to the frequency and severity of its complications, which represent the first cause of hospital admission, death and liver transplantation in patients with cirrhosis. Cirrhotic portal hypertension is a vascular disease which involves several systems and organs [12]. The main manifestations are briefly summarized in this section.

Splanchnic vascular bed. Cirrhosis causes marked alteration in this territory, featuring splanchnic vasodilation, decreased responsiveness to vasoconstrictors and formation of new blood vessels (angiogenesis) which contribute both to increase of splanchnic blood flow (arteriolar-capillary network), and portal–systemic collaterals [13] such as *gastro-oesophageal varices*, portal hypertensive gastropathy and colopathy, which are responsible for variceal bleeding episodes. Portal–systemic shunting is also involved in portal–systemic encephalopathy and other complications.

Systemic circulation. Portal hypertension is typically associated with a *hyperkinetic syndrome*, characterized by hypervolemia, increased cardiac index, hypotension and decreased systemic vascular resistance [14]. The hyperkinetic syndrome leads to a situation of hypotension and "effective" hypovolemia, volume receptors being stimulated despite the increased circulating blood volume. This leads to a marked activation of neurohumoral vasoactive factors in an attempt to maintain the arterial blood pressure within normal values, which plays a leading role in the pathophysiology of *ascites* and renal dysfunction in chronic liver disease [15]. Once ascites has formed, it can get infected by enteric bacteria which translocate from the bowel, causing *spontaneous bacterial peritonitis*.

Kidney. Renal abnormalities in cirrhosis are mostly functional, and characterized by marked renal vasoconstriction, responsible for the development of *hepatorenal syndrome*. As mentioned, renal vasoconstriction develops as a consequence of the splanchnic vasodilation and systemic hyperkinetic syndrome [15]. These concepts had provided the rationale for treating the hepato-renal syndrome with albumin infusion and vasoconstrictors (terlipressin, norepinephrine or midodrine) [16].

Lung. Vasodilatation in the lung leads to ventilation perfusion mismatch and even to A–V shunts in the pulmonary circulation; these determine the *hepatopulmonary syndrome*, characterized by marked hypoxemia [17,18]. In some cases, this may evolve into the opposite situation, *porto-pulmonary hypertension*, characterized by a marked increase of pulmonary vascular resistance [19]. The latter is thought to develop through endothelial dysfunction and vascular remodelling of the pulmonary circulation [20].

Heart. Portal hypertensive patients typically show a chronically increased cardiac output. Some patients exhibit electrophysiological changes such as QT prolongation and impaired ventricular contractility in response to both physiological and pharmacological stimuli. This constellation of cardiac abnormalities is termed "cirrhotic cardiomyopathy" [21]. In terminal stages of cirrhosis, especially in patients with sepsis and/or hepato-renal syndrome the cardiac output may decrease, which may be of clinical relevance contributing to further aggravate renal failure [22]. To what extent this is caused by the cirrhotic cardiomyopathy or by the release of cardiodepressing cytokines prompted by sepsis remains uncertain.

Blood abnormalities. Thrombocytopenia, leucopoenia and anaemia are frequent findings in portal hypertensive patients. Increased portal pressure plays a central role leading to *splenomegaly*, with consequent pooling and sequestration (the so-called hypersplenism) of corpuscular elements of the blood, predominantly thrombocytes. Moreover, liver failure reduces the hepatic synthesis of lineage-specific cytokine thrombopoietin (TPO), leading to reduced thrombopoiesis in the bone marrow and consequently to thrombocytopenia [23].

Brain. Changes in cerebral blood flow and vascular reactivity associated with portal hypertension are thought to facilitate some of the brain abnormalities of hepatic encephalopathy.

Skin. Advanced cirrhosis is characterized by warm skin, bounding pulses and palmar erythema, which all reflect the participation of the peripheral circulation in the hyperkinetic syndrome. In addition, dermal angiogenesis gives raise to the spider angioma characteristic of advanced liver disease. Hepatopulmonary syndrome may cause finger clubbing.

2. Natural history and prognosis of gastro-oesophageal varices

Variceal bleeding is the last step in a chain of events initiated by an increase in portal pressure, followed by the development and progressive dilation of varices until these finally rupture and bleed. It has been estimated that varices are present in about 30–40% of compensated patients at the time of diagnosis, and in 60% of decompensated patients [4,24,25]. In cirrhotic patients without varices at first endoscopy the annual incidence of new varices is 5–10% in published series [26–28].

Varices may appear when HVPG increases above 10 mm Hg [4,29]. A HVPG over 10 mm Hg is a strong predictor for the development of varices [4].

Once developed, varices usually increase in size from small to large before they eventually rupture and bleed. The reported rate of progression is heterogeneous (5–30% per year) [27,28,30,31]. The factor that has been most consistently associated with variceal progression is liver failure, as assessed by Child-Pugh class

[27,28,30,32]. Other factors include alcoholic aetiology of cirrhosis and presence of red wale markings at the varices [28,31]. Changes in HVPG (either "spontaneous" or caused by drug therapy or TIPS) are usually accompanied by parallel variations in the size of the oesophageal varices, which are significantly reduced when HVPG decreases below 12 mm Hg [6,33].

In patients with cirrhosis the overall incidence of variceal bleeding is about 4% per year. This risk increases to 15% per year in patients with medium–large varices [25]. The most important predictive factors related to the risk of bleeding are variceal size, Child-Pugh class and presence of red signs [34]. In addition, many studies have shown that variceal bleeding only occurs if the HVPG reaches a threshold value of 12 mm Hg [5,6,29]. Conversely, if the HVPG is substantially reduced (below 12 mm Hg or by more than 20% of baseline levels) there is a marked reduction in the risk of bleeding [6,35], thus demonstrating that the portal hypertension syndrome might be reversed if portal pressure is sufficiently reduced.

3. Treatment strategies and scenarios

3.1. Aims and rationale

Once portal pressure increases above a critical threshold value complications of portal hypertension can appear. Varices do not develop until the hepatic venous pressure gradient (HVPG), increases to 10–12 mm Hg, and it should be of at least 12 mm Hg for the appearance of other complications, such as variceal bleeding or ascites [5,29,36]. Longitudinal studies have demonstrated that if HVPG decreases below 12 mm Hg by means of pharmacological treatment [37], alcohol withdrawal or spontaneously due to an improvement in liver disease [33], variceal bleeding is totally prevented and varices may decrease in size. Besides, even if this target is not achieved, a 20% decrease in portal pressure from baseline levels (or greater) also offers a marked protection from variceal bleeding [37]. Furthermore, achievement of these targets may be associated with a lower risk of developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and death [38], thus demonstrating the reversibility of the portal hypertensive syndrome. These findings provide the rationale for treatments aimed to reduce portal pressure in patients with portal hypertension.

3.2. Therapeutic reduction of portal pressure

In cirrhosis, increase in vascular resistance to portal blood flow at the hepatic microcirculation is the initial factor leading to portal hypertension. Contrary to what was traditionally thought, this increased hepatic vascular resistance is not only a mechanical consequence of the hepatic architectural distortion caused by fibrosis, nodule formation, sinusoidal remodelling and vascular occlusion characteristic of cirrhotic, but there is also a dynamic component, due to the active contraction of portal/septal myofibroblasts, activated hepatic stellate cells and vascular smooth muscle cells in portal venules [39–41] which is due to an imbalance between increased vasoconstrictor stimuli in the presence of impaired vasorelaxating mechanisms [42]. Thus, in cirrhotic liver there is an increase in the activity of several endogenous vasoconstrictors such as endothelin, leukotrienes or thromboxane A_2 among others [43] and a reduced nitric oxide bioavailability [39,44–46] (Fig. 1). It is estimated that about one-third of the increased resistance to portal blood flow through the cirrhotic liver is due to this dynamic component.

Reducing intrahepatic resistance either by improving the architectural abnormalities or by reducing the increased hepatic vascular tone of the cirrhotic liver will decrease portal pressure. Such an approach would have the additional advantage of improving liver perfusion and thereby, liver function.

Improvement in liver architecture may be achieved using drugs or cell therapy to prevent/reverse sinusoidal remodelling and fibrogenesis [15] or by specific treatments for the underlying liver disease (interferon and antivirals for chronic hepatitis C and B, iron depletion for haemochromatosis, copper chelation for Wilson's disease, and alcohol abstinence for alcoholism). For each of these treatments there is evidence showing reduction in portal pressure with successful therapy [16,17].

Restoring the equilibrium between vasodilator and vasoconstrictor forces within the liver circulation would reduce the hepatic vascular tone and resistance of the cirrhotic livers. This could be achieved by improving intrahepatic NO availability by means of increasing its production either by NOS [47] or aAKT [48] gene-transfer; by the development of liver-specific NO-donors [49,50]; by posttranslational upregulation of eNOS using statins [51,52] or tetrahydrobiopterin supplementation [46], and by preventing NO scavenging using anti-oxidant [53] or SOD gene-transfer [54]. Other potential approaches are the inhibition of the vasoconstrictor system COX-1/TXA2 pathway [55–57] or increasing H2S [58].

The increased resistance through the cirrhotic liver can also be targeted by "mechanical" means, bypassing the liver. This can be achieved by portal–systemic shunt surgery and by transjugular intrahepatic portal–systemic 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.
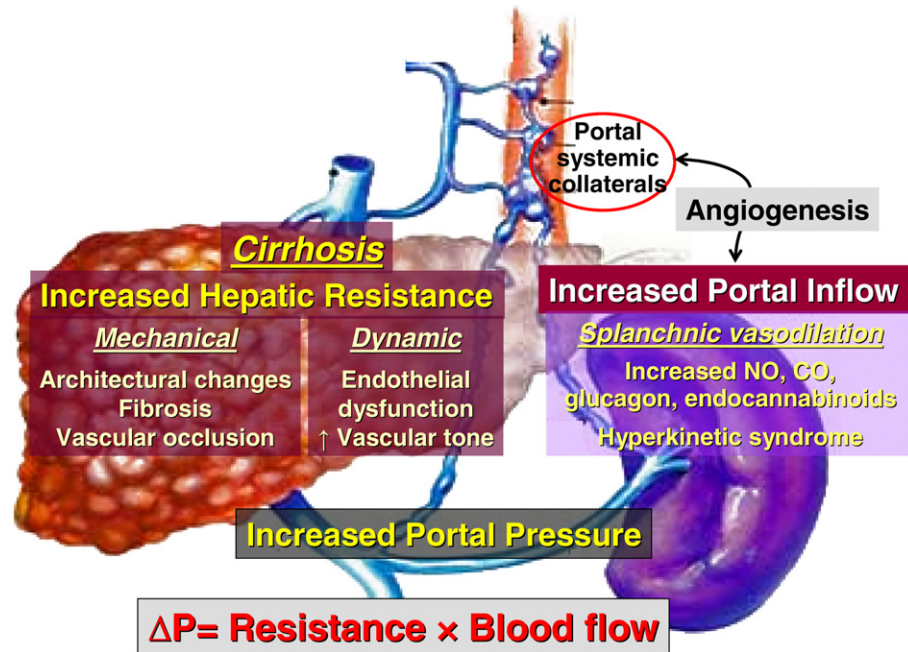
Fig. 1. Pathophysiology of portal hypertension: the different contributors to the increased portal pressure represent specific targets for therapy. Current treatments are all based on correcting the increased portal inflow. New treatments acting on the remaining determinants of portal hypertension are being actively investigated.

A second factor contributing to portal hypertension is an increased blood flow through the portal venous system due to splanchnic arteriolar vasodilatation. This is caused by an excessive release of endogenous vasodilators (endothelial and neuro-humoral) [59–63]. Splanchnic hyperaemia contributes to aggravating the increase in portal pressure and explains why portal hypertension persists despite the establishment of an extensive network of portal–systemic 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 more widely been used in the treatment of portal hypertension. Splanchnic vasodilatation is in part due to an increased release of NO, which is amendable to pharmacological manipulation. However, this faces the difficulty of inhibiting NO synthesis only in the splanchnic circulation, which is not feasible at present.

Splanchnic vasodilatation is accompanied by increased cardiac index and hypervolemia, representing the hyperkinetic circulatory syndrome associated with portal hypertension [15,64]. 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 [65].

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 [66]. Table 2 summarizes the different drugs and its dose that have been shown to reduce portal pressure in cirrhosis.

Recent studies have demonstrated that VEGF/PDGF mediated angiogenesis plays a relevant role in sinusoidal remodelling and liver fibrogenesis, in the formation of portal–systemic collaterals and in the development of a hyperkinetic splanchnic circulation [67,68]. Studies blocking VEGF by a variety of approaches have shown that this is associated with a decreased formation of portal–systemic collaterals and to reduced porto-collateral blood flow. Furthermore, the combined blockade of VEGF and PDGF results in a marked fall in portal pressure. Even in conditions not decreasing portal pressure VEGF blockade may prevent collateralization by over 50% [13,67]. This is a new concept, challenging the traditional hypothesis that formation of collaterals (including varices) was only the result of the dilation by the increased portal pressure of pre-existing but functionally closed vascular channels at sites of communication between the portal and systemic circulation, and emphasizes that antagonizing angiogenesis may represent a new therapeutic target for portal hypertension [42,69].

3.3. Local treatments

In addition to pathophysiological oriented treatments, there are several other approaches that have been

Table 2
Drugs used to reduce portal pressure in cirrhosis and their dosage

Drug	Administration	Dose	Period of administration
Vasopressin (VP) + nitroglycerin (NG)	VP: i.v. infusion NG: percutaneous	VP: 0.4 uu/min NG: 20 mg	2–5 days (acute bleeding)
Terlipressin	i.v. boluses	2 mg/4 h for 24–48 h then 1 mg/4 h	2–5 days (acute bleeding)
Somatostatin	i.v. bolus then i.v. infusion	250 mcg followed by 250–500 mcg/h	2–5 days (acute bleeding)
Octreotide	i.v. bolus then i.v. infusion	50 mcg followed by 50 mcg/h	2–5 days (acute bleeding)
Vapreotide	i.v. bolus then i.v. infusion	50 mcg followed by 50 mcg/h	2–5 days (acute bleeding)
Propranolol (non-selective BB)	Oral	20 mg bid; increase the dose up to the maximum tolerated (maximum 320 mg/day)	Chronic (primary and secondary prophylaxis)
Nadolol (non-selective BB)	Oral	40 mg bid; increase the dose up to the maximum tolerated (maximum 160 mg/day)	Chronic (primary and secondary prophylaxis)
Carvedilol (non-selective BB with alfa-blocker activity)	Oral	6.25 mg bid; increase the dose up to the maximum tolerated (maximum 50 mg/day)	Chronic (primary and secondary prophylaxis)
Isosorbide mononitrate	Oral	10–20 mg bid; increase up to 20–40 bid if tolerated	Chronic, only in association with BB (primary and secondary prophylaxis)

shown to be useful in the treatment of bleeding related to portal hypertension.

Endoscopic treatments are directed at 'eradicating' the varices either by 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 its effects are of limited duration. Local treatments have no effect on other complications of portal hypertension. Moreover, it is possible that the efficacy of endoscopic therapy can be enhanced if combined with an agent that effectively lowers portal pressure [70]. However, if the decrease in portal pressure gradient is greater than 20% of baseline or to values below 12 mm Hg there is probably no need for associating any invasive endoscopic procedures.

Balloon tamponade may temporarily control bleeding in 60–90% of patients. However, on deflation of the balloons, bleeding recurs in about 50% of cases [71]. Balloon tamponade is used only for 12–24 h in emergency situations as a bridge to definitive therapy if drugs and endoscopy fail to control variceal bleeding. Severe complications occur in 10–15% of patients and consist mainly of aspiration pneumonia and, rarely, oesophageal rupture. Complication-related mortality ranges between 2% and 5%. Only well-trained personnel should attempt tamponade [71].

Expandable oesophageal stents. It has been recently suggested in a small series of cirrhotic patients with uncontrolled bleeding from oesophageal varices that the implantation of covered expandable oesophageal stents may be a safe and effective alternative to balloon tamponade [70,72]. These promising results will have to be confirmed in comparative studies including larger number of patients.

Hemostatic agents, such as recombinant activated factor VII, are being explored as adjuvants to conven-

tional therapy to arrest variceal bleeding in patients with poor liver function [73,74].

3.4. Clinical scenarios for treatment

The treatment of portal hypertension takes place in different scenarios, which go from the asymptomatic patient who has never bled from varices, to the treatment of the acute variceal bleeding episode and the prevention of recurrent bleeding. The main difference between these scenarios is that natural history and prognosis is very different from one to another. This knowledge of the natural history of each of these situations should guide the selection of therapies, since the efficacy of the available treatments is inversely proportional to their invasiveness and adverse effects.

4. The compensated patient: prevention of first bleeding

4.1. Who should be treated? Diagnosis and screening policy

4.1.1. Screening for varices: when and how

The main aim for screening patients for oesophageal varices is to detect those requiring prophylactic treatment. In addition, the appearance of varices in compensated cirrhotic patients identifies a change from a clinical stage with a very low risk of death at 1 year (*stage 1*; 1% risk) to an intermediate risk stage (*stage 2*; 3.4% risk) [75]. Therefore, the current consensus is that every cirrhotic patient should be endoscopically screened for varices at time of diagnosis [27]. In patients without varices on initial endoscopy, a second (follow-up) evaluation should be performed after 2–3 years [70]. High-risk varices call by prophylactic treatment. They include "large"

varices (over 5 mm in diameter) and small varices with red colour signs or in a Child-Pugh class C patient. Since endoscopy is somehow invasive, and not all patients agree to adhere to repeated endoscopic evaluations, non-invasive substitutes for endoscopy have been proposed. Unfortunately, none of the available non-invasive tests has proved to be accurate enough as to avoid endoscopy in patients with negative indicators [76,77]. However, some clinical, laboratory and imaging variables may help in selecting the group of patients at high risk for varices [78,79].

Non-invasive tests

Physical examination. Physical stigmata of cirrhosis are a palpable firm left hepatic lobe [80], gynaecomastia, testicular atrophy, parotidomegaly, jaundice, vascular spiders, leuconykia, palmar erythema, signs of hepatic encephalopathy, presence of abdominal wall collateral circulation, ascites, leg oedema and splenomegaly (which may be considered the single most important diagnostic sign of portal hypertension). In addition, hypotension, bounding pulses, and tachycardia, reflect the hyperdynamic circulation. A systematic review of the diagnostic accuracy of physical examination for the detection of cirrhosis found that all these physical findings are highly specific [81]. However these findings are more common in decompensated disease. The sensitivity of physical signs is much lower in compensated cirrhosis, where non-invasive diagnosis would be more valuable.

Clinical/biological markers of CSPH. Child-Pugh score has been shown to correlate with portal pressure [82–84] and with the prevalence and grade of oesophageal varices. In patients with cirrhosis, platelet count was independently correlated with the prevalence and grade of oesophageal varices in several studies, although its predictive value is far from ideal [85–87]. Giannini et al. showed that platelet count/spleen diameter ratio above 909 has a 100% negative predictive value for the presence of oesophageal varices [79]. This index may help in reducing the number of endoscopies for the screening of oesophageal varices.

Imaging techniques

Ultrasound and duplex-Doppler. Splenomegaly (spleen length >13 cm) is the ultrasonographic finding more frequently associated with portal hypertension and with oesophageal varices. Other US-Doppler measurements, related with portal hypertension include: dilated portal vein (diameter above 13 mm) [88]; lack or reduced respiratory variations of splenic and superior mesenteric vein diameter [89]; reversal of portal blood flow; reduced portal vein velocity (maximal and mean velocimetry of portal vein flow, respectively, <20 cm/s and <10–12 cm/s) [90]; increased congestion index of portal vein [91]; presence of portal–systemic collateral circulation [92]; altered hepatic venous Doppler pattern [93], increased

intraparenchymal hepatic and splenic artery impedance [94–96]; increased intraparenchymal renal artery impedance [97] and reduced mesenteric artery impedance [98]. Besides, US-Doppler is very useful to assess portal vein patency.

Other imaging techniques. Computed tomographic scan (CT) and magnetic resonance (MRI) allow an accurate visualization of portal venous system. Recently, dynamic contrast-enhanced single-section CT scans and MRI (compartmental analysis of intensity versus time curves for magnetic resonance images of the liver after injection of a gadolinium chelate) and phase contrast MR angiography have been described to permit an observer independent quantitative measurement of portal [99] and azygos [100] blood flow. Portal fraction of liver perfusion and mean transit time at MRI have been suggested to correlate with HVPG [101]. However, whether any of these rather expensive techniques add significantly to clinical, biochemical or US parameters is not known.

Elastography. Liver stiffness measurement by transient elastography (*FibroScan*®) is a new non-invasive method based on the measurement by means of an ultrasonographic transducer of the velocity of propagation of a low frequency vibration wave. The velocity of propagation of the wave is directly related to the tissue stiffness, which correlates with fibrosis in liver disease [102,103]. Liver stiffness has been shown to predict cirrhosis in different studies, with good accuracy but with different cut-offs depending on the underlying aetiology. Liver stiffness measurements have been recently evaluated for the prediction of CSPH, since up to 40% of compensated cirrhotic patients do not have CSPH [4] and could safely avoid endoscopic screening. Liver stiffness showed an excellent correlation with fibrosis and with HVPG in patients with recurrent HCV infection after OLT [104]. In this study, a liver stiffness value ⩾ 8.74 kPa had a sensitivity and specificity of 90% and 81% for the diagnosis of portal hypertension (HVPG ⩾ 6 mm Hg). In cirrhosis, liver stiffness has been shown to correlate with the presence of large oesophageal varices [105]. A liver stiffness >19 kPa predicted the presence of large oesophageal varices. Yet, other values have been proposed by other studies [106]. Two recent studies showed that the cut-off values of 23 and 13.6 kPa have a good capacity to predict the presence of CSPH in patients with chronic liver disease [107,108], but above the threshold value of 13.6 kPa the correlation between liver stiffness and HVPG was poor, suggesting that once portal–systemic collaterals develop, structural abnormalities within the liver (e.g. fibrosis) are no longer the main determinant of portal hypertension.

Thus, it appears that the finding of a high value of liver stiffness (the cut-off still not well defined) has potential to predict cirrhosis and probably the presence

of CSPH. However, the technique is not adequate to assess portal pressure in advanced stages. Other limitations of liver stiffness measurements are that it cannot be used in obese or ascitic patients, and that liver inflammation increases the values independently of the degree of fibrosis.

MR elastography is a novel method proposed to evaluate liver stiffness. The measurement is obtained by synchronizing motion-sensitive imaging sequences with the application of acoustic waves in tissue media [109]. Preliminary results support its practicability in predicting the stage of fibrosis in patients with chronic liver disease [110]. MR elastography has technical advantages over Fibroscan (no need for an acoustical window, a freely-oriented field of view, and the insensitivity to obesity), but it is much more expensive and time consuming.

Procedures

Endoscopy. Upper gastrointestinal endoscopy is mandatory in patients with cirrhosis in whom portal hypertension is suspected. It allows the assessment of the presence and size of oesophageal and gastric varices, the presence of red signs in the variceal wall and the presence and severity of portal hypertensive gastropathy. The use of conscious sedation markedly increases the patients' compliance to the procedure.

Endoscopic videocapsule. This has been recently introduced as it may improve patients' tolerance. Once swallowed, the videocapsule records images at pre-determined intervals. In the two published studies, capsule endoscopy allowed a correct identification of varices in 80% of cases [111,112]; in one of these studies capsule endoscopy allowed the identification of red wale marks [111]. However it may not be as good in assessing variceal size and it may have poor accuracy in identifying the presence of hypertensive gastropathy and that of gastric varices [113]. Further data is required before it could be recommended for the routine screening of varices in patients with cirrhosis.

HVPG measurement. HVPG measurement is the gold standard technique to evaluate the presence and severity of portal hypertension. Measurement of HVPG at hepatic vein catheterisation is an objective and quantitative equivalent of portal pressure in cirrhosis [2]. HVPG has proved to add prognostic information in many settings, including compensated cirrhosis, acute variceal bleeding [114], and patients awaiting liver transplantation [115]. Patients with CSPH are at high risk of varices and should undergo endoscopic screening. Furthermore, changes in HVPG during therapy provide robust prognostic information (see below).

4.1.2. Who should be treated?

As previously discussed, the current consensus is that every cirrhotic patient should be endoscopically screened for varices at time of diagnosis [27]. In patients without varices on initial endoscopy, a second (follow-up) evaluation should be performed after 2–3 years [70]. Since endoscopy is unpleasant for the patient, and screening in all cirrhotic patients is a substantial burden empirical beta-blocker therapy for all patients has been proposed. Two studies suggest that this strategy is cost effective [116,117], but a third suggested that this strategy is cost effective only in patients with decompensated cirrhosis [118].

Patients without varices. Based on results in experimental models of portal hypertension [119] non-selective beta-adrenergic blockers were proposed for the prevention of the development of varices. To test this hypothesis, in a large multicenter study 213 patients with cirrhosis and portal hypertension (HVPG > 5 mm Hg) but without varices were randomised to receive timolol or placebo in double-blind conditions for a median of 55 months [4]. The primary endpoint was development of oesophageal varices or variceal haemorrhage. The rate of development of the primary endpoint did not differ between the two treatment groups and adverse events were more frequent in the timolol group. Therefore, beta-adrenergic blockers cannot be recommended for the prevention of the development of oesophageal varices. Recent studies have shown that blockade of the vascular endothelial growth factor (VEGF) signalling cascade is highly effective reducing the formation of collaterals in experimental models [13,67], but no study has explored this clinically. As already discussed, a different approach is to prevent the progression of cirrhosis (i.e. abstinence in alcoholics, antivirals in viral cirrhosis, lifestyle change in NASH, corticosteroids in autoimmune hepatitis, phlebotomies in haemochromatosis, copper chelators in Wilson's disease).

Patients with high-risk varices. In the past only patients with medium to large varices were considered for prophylactic treatment of variceal bleeding. This was due to the fact that most studies with beta-adrenergic blockers were performed in patients with medium to large varices, while the beneficial effects of beta-blockers are less clear in patients with small varices [120]. However, the classification of varices according to their size is subjective and at the recent Baveno IV consensus conference it was not possible to agree on a clear definition of small and big varices [70]. On the other hand, it is well established that "small" (F1) varices with red signs or in Child-Pugh C class patients have a bleeding risk similar to that of big varices [34]. Also, beta-adrenergic blockers may reduce the rate of progression from small to large varices, and decrease the incidence of variceal bleeding in patients with small varices [27]. Thus, current guidelines recommend initiating beta-blockers in patients with high-risk varices. These include patients with moderate to large varices, and patients with small varices with red signs or Child-Pugh C [70]. No follow-up endoscopy is needed once the patient is under beta-blockers. If beta-blockers are not initiated in

patients with small varices, follow-up endoscopy should be performed every 1–2 years, or if the patient decompensates.

4.2. Treatments for the prevention of first bleeding: beta-adrenergic blockers vs endoscopic band ligation (Text Box 1)

Non-selective beta-adrenergic blockers (propranolol or nadolol) have been shown to reduce the risk of first variceal bleeding (from 24% to 15% after a median follow-up 2 years) and mortality (from 27% to 23%) [120]. It is important to note that beta-blockers are among the safest and cheapest drugs in Europe. However, circa 25% of cirrhotic patients with high-risk oesophageal varices may have either contraindications for the administration of non-selective beta-blockers or cannot tolerate these drugs. Additionally, the degree of protection (about 40% relative risk reduction on an intent-to-treat basis) is not ideal.

Text Box 1
Prophylaxis of first variceal bleeding: recommendations

- Patients without varices should be screened endoscopically for the appearance of varices every 2–3 years. In patients with small varices it is indicated to repeat endoscopy every 1–2 years. The interval should be shortened in patients with HVPG $\geqslant$ 10 mm Hg.
- Patients with moderate/large varices should be treated with a non-selective beta-blocker if there are no contraindications.
- Patients with small varices with red signs or with advanced liver failure (Child-Pugh C) are at similar risk of bleeding as those with moderate/large varices and should be considered for preventive therapy
- Patients with moderate/large varices with contraindications to or who cannot tolerate beta-blockers should be offered endoscopic band ligation. Band ligation might be used as first choice in patients with moderate/large varices depending on patient's preferences and local resources.
- If no bleeding occurs treatment should be maintained for life (unless the liver disease improves and significant portal hypertension disappears).

The addition of isosorbide 5-mononitrate (ISMN) significantly increases HVPG response to beta-adrenergic blockers [121]. However, it is less clear whether this translates into a greater clinical efficacy in primary prophylaxis. An open trial comparing nadolol vs nadolol + isosorbide mononitrate demonstrated a significant lower rate of first bleeding in the combination group, without survival advantage [122,123]. However, a large subsequent double-blind, placebo-controlled study failed to confirm these results [124].

Endoscopic band ligation (EBL) is effective in preventing the first variceal bleeding in patients with medium to large varices [125]. So far 17 trials have compared EBL with beta-blockers for the primary prevention of variceal bleeding [126–142]. The meta-analysis of these trials (both including or excluding the studies published as abstract) shows an advantage of EBL over beta-adrenergic blockers in terms of prevention of first bleeding, without differences in mortality [143,144]. These results, however, have several problems. Firstly, most trials were underpowered or lacked any sample size calculation (11 out of 17 included less than 100 patients when the sample size to detect a decrease in the incidence of variceal bleeding at 2 years from 20% under beta-blockers to a 12% with EBL under a two-sided hypothesis with alpha 0.05 and beta 0.20 would be of 658 patients). The largest trial to date included only 152 [128]. Additionally, four of the trials were prematurely stopped [128,133,134,141]. Fig. 2 shows a stratified meta-analysis of the available trials. Pooling the results from the 4 published trials that included more than 100 patients (with a total of 462 patients) shows no significant benefit of EBL over beta-blockers. The analysis of trials published as abstracts (520 patients) shows no benefit from EBL over beta-blockers with significant heterogeneity. Only in the subgroup of published trials with less than 100 patients (334 patients) there was a significant benefit from EBL. This illustrates that available evidence to favour EBL over beta-blockers is very weak.

Another source of controversy is the higher incidence of adverse events in patients treated with beta-blockers than with EBL [144]. In this regard, it should be noted that while most side effects related to beta-blockers (hypotension, tiredness, breathlessness, impotence, insomnia) were easily managed by adjusting the dose or discontinuing the drug, patients did not require hospital admission and no fatalities were observed [143], side effects related to EBL are of much greater significance, since most are bleeding episodes directly related to the procedure, that frequently required hospitalization and blood transfusion and resulted in three deaths [128,141]. Further, long-term safety and benefits of prophylactic EBL are still uncertain. On the contrary, long-term safety and efficacy of non-selective beta-adrenergic blockers are well established [145,146].

Cost-effectiveness of EBL vs beta-blockers for primary prophylaxis has been compared in three decision-analysis studies with conflicting conclusions, probably due to different assumptions on the incidence of variceal bleeding, quality of life with each treatment and other portal hypertensive complications [116,118,147]. Another variable to consider is patient's and physician preferences. A recent study evaluated predicted preferences from patients and physicians with an interactive computer task. Sixty-four percent of the

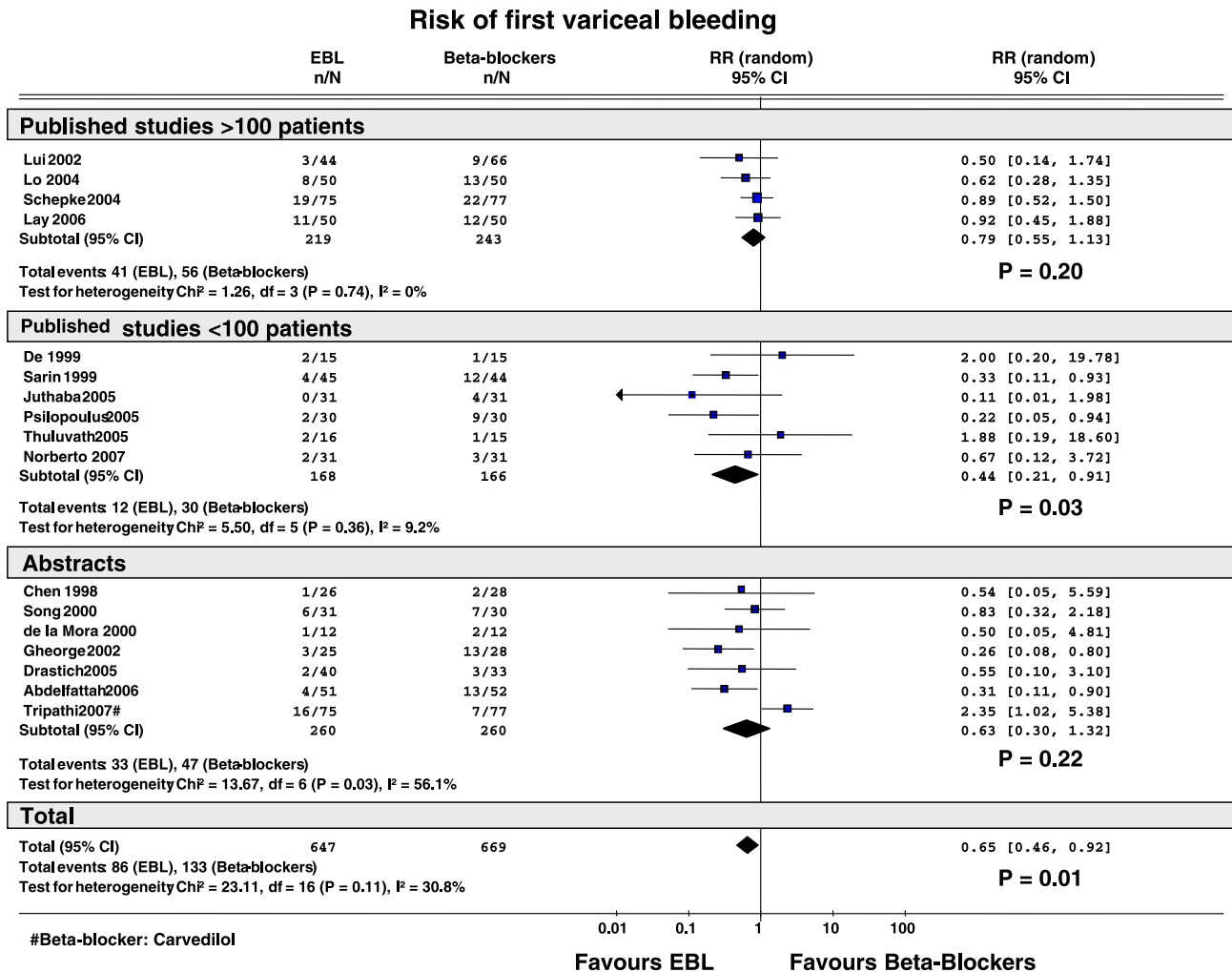## Risk of first variceal bleeding

Fig. 2. Meta-analysis (random effects model) of randomised controlled trials comparing endoscopic band ligation (EBL) with beta-adrenergic blockers in the prevention of first variceal bleeding. The studies have been pooled in three groups: published studies that included more than 100 patients, published studies but with less than 100 patients, and abstracts.

patients preferred EBL, based mainly on the possibility of shortness of breath and hypotension [148], although the option of switching from beta-blockers to EBL in case of side effects was not considered in the algorithm.

The recommendation made at the 2005 Baveno consensus conference is that non-selective beta-blockers should be considered as first-choice treatment to prevent first variceal bleeding in patients with high-risk varices, while EBL should be offered to patients with contraindications or intolerance to beta-blockers [70] (Text Box 1). The recently published guidelines by the AASLD and the ACG consider beta-blockers as first choice in patients with medium/large varices that have not bled and are not at the highest risk of haemorrhage (Child A patients and no red signs), but in high-risk patients both EBL and beta-blockers are considered first choice [149].

The combination of pharmacology and endoscopic therapy has been investigated with contrasting results. In one study band ligation plus beta-adrenergic blockers

offered no benefit in terms of prevention of first bleeding when compared to band ligation alone [150]. In a more recent study combination therapy significantly reduced the occurrence of the first episode of variceal bleeding and improved bleeding-related survival in a group of cirrhotic patients with high-risk oesophageal varices in the waiting list for liver transplantation [140]. Probably more studies would be required, although these are unlikely to be performed due to the very large number of patients that would be needed.

4.3. Unanswered issues

4.3.1. HVPG monitoring. Is it worth it? What is its target?

Longitudinal studies have demonstrated that a decrease in HVPG < 12 mm Hg essentially eliminates the risk of bleeding and improves survival [6], while reductions >20% from baseline [146,151] or even >10% from baseline [152] significantly decrease the risk of first

variceal bleeding. This leads to the question on whether HVPG measurements should be used to monitor response to drug treatment in clinical practice. Two simulation analyses have yielded conflicting results, one suggesting that HVPG monitoring might be cost effective in primary prophylaxis [153], and the other arriving to the opposite conclusion [154]. The main problem is that the assumptions of these analyses (i.e. how to manage non-responders to medical treatment) have never been tested in randomised controlled trials. A recent study of HVPG guided therapy suggested that the shift of non-responders from beta-blockers to EBL does not improve the outcome [155]. The issue will remain hypothetical until HVPG guided therapy is proven better than empirical approaches in randomised controlled trials.

4.3.2. Endoscopic treatment: how frequent, how to monitor the treatment

There is no agreement on how frequently the varices should be ligated in the initial course of eradication, the interval varying from 1 to 4 weeks [128,133]. A recent trial evaluated the effectiveness and complications of EBL every two weeks vs every two months. This trial included patients with and without previous bleeding, though most patients were treated for primary prophylaxis [156]. The two-month interval scheme obtained a higher total eradication rate and lower recurrence rate. No patient in either group bled. Thus, although admittedly weak, current evidence favours monthly intervals. This might not apply to prophylaxis of recurrent bleeding (in which the risk of rebleeding is maximal in the first few weeks) where a 1–2 week interval might be more appropriate. Once the varices are eradicated, follow-up endoscopies should be performed at 1–3 months and every 6 months thereafter, and varices should be re-eradicated upon recurrence. This is in marked contrast with prophylaxis with beta-blockers, in which no follow-up endoscopies are needed.

5. Prevention of recurrent bleeding from oesophageal varices

Patients surviving a first episode of variceal bleeding have a risk of over 60% of experiencing recurrent haemorrhage within two years from the index episode. Because of this, all patients surviving variceal bleeding should receive active treatments for the prevention of rebleeding [70].

Available treatments for preventing variceal rebleeding include pharmacological therapy, endoscopic therapy, TIPS and surgical shunting (Fig. 3).

Pharmacological therapy. Non-selective beta-blockers are the first-line pharmacological therapy for the prevention of rebleeding [70]. Several meta-analyses have consistently found a marked benefit of beta-blockers showing a reduction in rebleeding rate from 63% in controls to 42% in treated patients [120]. Notably, beta-blockers also

induce a significant decrease of overall mortality from 27% to 20% [120] and of mortality due to bleeding [157].

Beta-blockers have been compared with endoscopic variceal sclerotherapy in the prevention of rebleeding. No significant differences were found either for rebleeding or for mortality but side effects were significantly less frequent and severe with beta-blockers [120].

The combination of *propranolol or nadolol plus 5-isosorbide mononitrate (ISMN)* enhances the reduction of portal pressure induced by non-selective beta-blockers [121]. There is only one published study comparing ISMN associated with propranolol [158] vs propranolol alone in the prevention of rebleeding. The study showed a significant benefit of the pharmacological association. The association of propranolol/nadolol and ISMN has been compared with endoscopic sclerotherapy [159] showing less rebleeding in the pharmacological treatment arm, and with band ligation (EBL) in 4 studies [160–163]. A meta-analysis of the 4 studies vs EBL have shown no significant differences between both treatments in preventing rebleeding or in mortality. The association of beta-blockers and ISMN seems to be the best pharmacological approach to prevent rebleeding [149].

Endoscopic treatment is a local treatment aimed at eradicating the varices. Since it does not decrease on portal pressure, varices may recur after endoscopic treatment, and patients need to receive a life-long endoscopic follow-up to detect variceal recurrence.

Endoscopic injection sclerotherapy of oesophageal varices significantly reduces both the rebleeding and death risk. It takes 4–6 endoscopic sessions to eradicate varices, but recurrence of varices occurs in nearly 40% of patients within one year from eradication. The most serious side effects of therapy are dysphagia, oesophageal stenosis and bleeding from oesophageal ulcers, which may account for as much as 14% of all the rebleeding episodes. As commented above, sclerotherapy has no advantage over drug therapy and causes more frequent and severe side effects, and has been abandoned since the advent of EBL.

Endoscopic banding ligation (*EBL*) is clearly superior to sclerotherapy [143], due to less frequent and severe complications. Thus, EBL is at present the endoscopic treatment of choice [70]. Variceal eradication is achieved with a lower number of EBL sessions than with sclerotherapy, but EBL is associated with higher rate of recurrence of varices [143].

Combined endoscopic treatment: Sclerotherapy has been added (either simultaneously or after the reduction of variceal size to small) to EBL and compared to EBL alone. Meta-analysis of these studies does not show any benefit either for rebleeding or for mortality, and it also shows a trend towards an increasing complication rate with combination endoscopic therapy [164]. Therefore, there is no rationale to combine both endoscopic approaches.
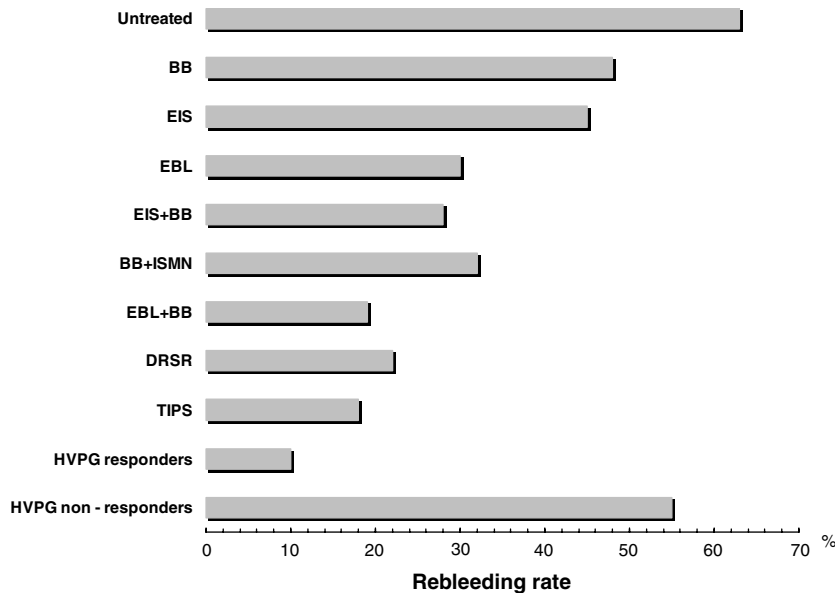
Fig. 3. Prevention of variceal rebleeding: rebleeding rates with different treatment options. The bars represent median values from data reported in meta-analysis. Note the extremely low rebleeding rate in patients treated with beta-blockers and who are HVPG "responders" (fall in HVPG of at least 20% of baseline and/or to 12 mm Hg or below).

Combined endoscopic and pharmacological treatment. The combination of the best endoscopic treatment (EBL) and the best pharmacological treatment (beta-blockers + ISMN) may be the best choice in prevention of rebleeding [70,165] (Text Box 2).

Text Box 2
Treatment of acute variceal bleeding: recommendations

- The best approach is the combined use of a vaso-active drug, started from admission (or even during transferral to hospital) and an endoscopic procedure.
- Terlipressin, somatostatin, octreotide and vasopressin + nitroglycerin (in this order of preference) may be used. Drug therapy should be maintained for 2–5 days.
- Endoscopic band ligation or injection sclerotherapy (in this order of preference) are the endoscopic treatments of choice in bleeding oesophageal varices. In bleeding gastric varices the best endoscopic choice is obturation with tissue adesives.
- Endoscopy (and endoscopic treatment) should be done within 12 h of admission.
- Prophylaxis of infection with broad spectrum antibiotics should be given to all patients

  TIPS should be used as a rescue procedure when medical and endoscopic therapies fail. Patients bleeding from gastric varices may require an earlier decision for TIPS.

The association of injection sclerotherapy and beta-blockers has been compared with either sclerotherapy or beta-blockers alone. The meta-analysis of the RCTs comparing combination therapy with sclerotherapy alone showed a significant reduction of the rebleeding risk with combination therapy, but no differences for mortality [24]. Also when compared with beta-blockers alone, combination therapy significantly reduced the rebleeding risk but without advantage for survival [120].

Two RCTs have shown that adding beta-blockers to EBL reduces the risk of rebleeding and variceal recurrence [166,167], suggesting that if EBL is used, it should be used in association with beta-blockers. A recent RCT, still published as an abstract [168], has evaluated whether EBL may improve the efficacy of the combined administration of nadolol + ISMN. In this study, adding band ligation to nadolol plus ISMN was shown to be superior to nadolol + ISMN alone in preventing variceal rebleeding, but there were no significant differences in mortality.

5.1. Pending problems

5.1.1. HVPG guided therapy in the prevention of rebleeding

Pharmacological (or spontaneous) reduction of HVPG to <12 mm Hg or by ≥20% of the baseline value (HVPG responders) decreases dramatically the risk of rebleeding and significantly reduces mortality [37]. The rebleeding risk in the group of responders is as low as that achieved using surgical shunts or TIPS [169]. As a consequence, adding further treatment (i.e. band ligation) in this group is unlike to enhance efficacy, but may increase severe side effects. On the other hand, it is still uncertain

whether patients with an insufficient hemodynamic response to pharmacological therapy (non-responders) would benefit from alternative treatments. In the study by Bureau et al. [155], HVPG non-responders to beta-blockers ± ISMN were shifted to receive endoscopic band ligation without any benefit. Preliminary data from a Spanish multicenter RCT comparing nadolol + ISMN vs Nadolol + ISMN + EBL[168] found no significant differences in rebleeding rates in HVPG non-responders treated with drugs alone or with drugs + EBL. These data suggest that EBL may not be the best alternative to reduce rebleeding in non-responders. Probably more effective and aggressive therapies are needed to reduce the high rebleeding risk of HVPG non-responders (46–65% in a recent survey[169]). Indeed, Gonzalez et al. showed a low rebleeding rate (19%) in HVPG non-responders treated with TIPS[170]. Unfortunately, the study did not include a control group. Thus, until more data are available HVPG guided therapy should only be used in the setting of clinical research.

5.1.2. The role of TIPS

TIPS has proven better than the combination of ISMN and propranolol [171], and to endoscopic therapy in the prevention of variceal rebleeding [172], with rebleeding rates of 9–23% for TIPS. However, as expected, the high effectiveness in preventing recurrent bleeding is associated with an increased risk of encephalopathy, without a survival benefit. Because of this, TIPS is considered as salvage therapy for patients who bleed despite adequate medical and endoscopic treatment. TIPS has been compared with surgical shunts in two RCTs (8 mm portocaval H-graft shunt in one, and distal splenorenal shunt (DSRS) in the second) [173,174]. The first study favoured surgical shunts, which showed a significantly lower rebleeding rate and a lower incidence of the composite end-point of rebleeding, shunt thrombosis, deaths, and need for transplant compared with TIPS. There was no difference in mortality. The second and larger trial [174] showed no significant differences in rebleeding rate (5.5% in the DSRS group, and 9% in the TIPS group), incidence of hepatic encephalopathy, liver transplantation or mortality. There was a significantly higher reintervention rate in the TIPS group (82%), which used bare stents, than in the DSRS group (11%). However, the obstruction and reintervention rates can be markedly decreased with the use of polytetrafluoroethylene (PTFE)-covered stents [175]. According to these data, TIPS using PTFE-covered stents represent the best rescue therapy for failures of medical and endoscopic treatment.

5.2. Prevention of rebleeding from gastric varices

Gastric variceal bleeding is relatively uncommon and there are few specific studies on its prevention. Type 1 gastric varices (GOV 1) are an extension of oesophageal varices along the lesser curvature of the stomach, and their management is the same as for oesophageal varices. Isolated gastric varices (IGV1) and fundal gastro-oesophageal varices (GOV 2), are those who present differential features. When IGV 1 are due to isolated splenic vein thrombosis splenectomy is a curative treatment. In acute bleeding from gastric varices, endoscopic variceal obturation (EVO) with *N*-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate (bucrylate) or thrombin has been shown to be more effective than sclerotherapy or EBL, and this extends to rebleeding [176–178].

Several papers demonstrated the effectiveness of TIPS in uncontrolled bleeding from gastric varices. In a recently published RCT [179], TIPS proved more effective than EVO in preventing rebleeding from gastric varices with similar survival and frequency of complications, despite the fact that TIPS stents were not PTFE-covered, and rebleeding rate after TIPS was much higher than previously reported, suggesting an inaccurate TIPS follow-up. Recent AASLD practice guidelines [149] advise the use of PTFE-covered TIPS for the prevention of the rebleeding from gastric varices in patients in whom bleeding recurs despite endoscopic and pharmacological therapy, even after a single failure has occurred. When patients do not present with acute bleeding (or have survived for some weeks a bleeding episode) non-selective beta-blockers are the usual treatment for the prevention of rebleeding, although there is limited information on its efficacy.

6. The acute bleeding episode

6.1. Natural history and prognosis

Ruptured oesophageal varices cause 70% of all upper gastrointestinal bleeding episodes in patients with portal hypertension [180]. Thus, in any cirrhotic patient with acute upper gastrointestinal bleeding, a variceal origin should be suspected. Diagnosis is established at emergency endoscopy based on observing one of the following: (a) active bleeding from a varix (observation of blood spurting or oozing from the varix) (near 20% of patients); (b) white nipple or clot adherent to a varix; (c) presence of varices without other potential sources of bleeding. Endoscopy should always be performed with 12 h of admission (preferable within 6 h).

Initial control of bleeding. Because variceal bleeding is frequently intermittent, it is difficult to assess when the bleeding stops and when a new haematemesis or melena should be considered an episode of rebleeding. Several consensus conferences have addressed this issue and set definitions for events and timing of events related to episodes of variceal bleeding [70]. Using these definitions, data from placebo-controlled clinical trials show

that variceal bleeding is spontaneously controlled in 40–50% of patients [120]. Currently available treatments increase control of bleeding at 5 days to about 80% of the patients [180].

Early rebleeding. The incidence of early rebleeding ranges between 30% and 40% in the first 6 weeks. The risk peaks in the first five days with 40% of all rebleeding episodes occurring in this very early period, remain high during the first 2 weeks and decline then slowly in the next 4 weeks. After 6 weeks the risk of further bleeding becomes virtually equal to that before bleeding [181]. Early rebleeding is a strong predictor of death from variceal bleeding. Prognostic indicators for early rebleeding (assessed in most studies as a composite with failure to control bleeding and five-day mortality) are summarized in Table 3A.

Mortality. The general consensus is that any death occurring within six weeks of hospital admission for variceal bleeding should be considered as a bleeding-related death [70]. This has greatly decreased in the last two decades, from 42% in the late 70s [181] to the current 15–20% [180,182–184]. Immediate mortality from uncontrolled bleeding is in the range of 4–8% [25,180]. Pre-hospital mortality from variceal bleeding might be around 3% [185]. Nowadays only 40% of the deaths are directly related to bleeding, while most are caused by liver failure, infections and hepatorenal syndrome [180]. Table 3B shows the most consistently reported risk indicators for 6-week mortality.

Table 3
Prognostic indicators, with their reported odds ratio/hazard ratio, for five-day treatment failure (A) and 6-week mortality (B), in patients with acute variceal bleeding

Variable	OR/HR	References
A: 5-day failure		
HVPG $\geqslant$ 20 mm Hg	5.4–11.4	[114,216,232]
Bacterial infection	4.6–9.7	[193,233,234]
Active bleeding at endoscopy	2.1–3.7	[180,193,235]
Portal vein thrombosis	3.1	[180,232]
Child-Pugh class	2.7	[180]
Child-Pugh score	1.2	[193]
Shock	4.9	[232]
AST levels (per IU increase)	1.003	[180]
B: 6-week mortality		
At admission		
Shock	5.8–9.9	[187,234]
Hepatocellular carcinoma	3.1–7.5	[180,236,237]
Hepatic encephalopathy	2.4–6.9	[180,234–236]
Active bleeding	5.4	[181]
Child-Pugh score	4.5	[233]
Prothrombin time, bilirubin, albumin	–	[180,235,237]
Creatinine, urea	–	[235,237]
Late prognostic indicators		
Renal failure	17.1–52.1	[187,236]
Bacterial infection	12.6	[234]
Early rebleeding	3.2–8.7	[235,236]

HVPG: hepatic venous pressure gradient.

6.2. Treatment of acute variceal bleeding

Acute variceal bleeding should be managed in an intensive care setting by a team of experienced medical staff, including well-trained nurses, clinical hepatologists, endoscopists, interventional radiologists, and surgeons [186]. Lack of these facilities demands immediate referral. Decision-making shall follow the guidelines set up in a written protocol developed to optimize the resources of each center.

6.2.1. General management

The general management of the bleeding patient is aimed at correcting hypovolemic shock (with judicious volume replacement and transfusion) and at preventing complications associated with gastrointestinal bleeding (bacterial infections, hepatic decompensation, renal failure), which are independent of the cause of the haemorrhage and demand immediate management. Initial resuscitation should follow the classic *Airway*, *Breathing*, *Circulation* scheme, and it is aimed at restoring an appropriate delivery of oxygen to the tissues (which depends on SaO_2 cardiac output and haemoglobin concentration). Airway should be immediately secured, especially in encephalopathic patients, since the patient is at risk of bronchial aspiration of gastric content and blood. This risk is further exacerbated by endoscopic procedures. Endothracheal intubation is mandatory if there is any concern about the safety of the airway.

Blood volume replacement should be initiated as soon as possible with plasma expanders, aiming at maintaining systolic blood pressure around 100 mm Hg. Avoiding prolonged hypotension is particularly important to prevent infection and renal failure, which are associated with increased risk of rebleeding and death [187]. Although it has been shown that volume expansion may induce rebound increases in portal pressure and rebleeding [188,189], the use of vasopressin analogues or somatostatin blunt the increase in portal pressure induced by volume expansion [190,191]. Thus, the use of vasoactive drugs allows a less conservative blood volume restitution policy. Blood transfusion should aim at maintaining the hematocrit at 0.21–0.24 (Hb 7–8 g/l) [70], except in patients with rapid ongoing bleeding or with ischemic heart disease. The role of platelet transfusion or fresh frozen plasma administration has not been assessed appropriately. The use of recombinant activated factor VII (rVIIa, Novoseven®), which corrects prothrombin time in cirrhotics [192], has been assessed in two randomised controlled trials. The first trial showed, in a post hoc analysis, that rFVIIa administration may significantly improve the results of conventional therapy in patients with moderate and advanced liver failure (stages B and C of the Child-Pugh classification) without increasing the incidence of adverse events

[73]. A more recent trial tested rVIIa in patients with active bleeding at endoscopy and with a Child-Pugh score ⩾8 points. This trial failed to show a benefit of rVIIa in terms of decreasing the risk of 5-day failure but improved 6-week mortality [74].

Infection is a strong prognostic indicator in acute variceal bleeding [193]. The most frequent infections are spontaneous bacterial peritonitis (50%), urinary tract infections (25%) and pneumonia (25%). The use of prophylactic antibiotics has been shown to reduce both the risk of rebleeding [194] and mortality [195]. Therefore, antibiotics should be given to all patients from admission. Quinolones are frequently used due to its easy administration and low cost [196]. In high-risk patients (hypovolemic shock, ascites, jaundice or malnutrition) i.v. ceftriaxone has recently been shown to be superior to oral norfloxacin [197].

Variceal bleeding can trigger hepatic encephalopathy. However, there are no data to support the prophylactic use of lactulose or lactitol [70].

6.2.2. Specific therapy for control of bleeding

Initial therapy for acute variceal bleeding is based on the combination of vasoactive drugs with endoscopic therapy. Rescue therapies for failures include balloon tamponade and portal–systemic shunts, either surgical or TIPS.

6.2.2.1. Pharmacological therapy. The action of vasoactive drugs is to reduce variceal pressure by decreasing variceal blood flow. 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 [120,198]. Somatostatin and somatostatin analogues (octreotide or vapreotide) are second choice [120,199]. If these drugs are not available vasopressin plus transdermal nitroglycerin is an acceptable option [120] (Table 2).

Terlipressin is a long-acting triglycyl lysine derivative of vasopressin. Clinical studies have consistently shown less frequent and severe side effects with *terlipressin* than with vasopressin (even if associated with nitroglycerin).

Terlipressin may be initiated as early as variceal bleeding is suspected at a dose of 2 mg/4 h for the first 48 h, and it may be maintained for up to 5 days at a dose of 1 mg/4 h to prevent rebleeding [200]. Compared with placebo or non-active treatment terlipressin significantly improves the rate of control of bleeding and survival [201]. This is the only treatment that has been shown to improve prognosis of variceal bleeding in placebo-controlled RCTs and meta-analysis [120,201]. Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy (EIS), and is safer than vasopressin+nitroglycerin and EIS [120,200,201]. The most common side effect of this drug is abdominal pain. Serious side effects such as peripheral or myocardial ischemia occur in less than 3% of the patients [200]. The overall efficacy of terlipressin in controlling acute variceal bleeding at 48 h is of 75–80% across trials [201], and of 67% at 5-days [200]. Terlipressin is also useful in hepatorenal syndrome [202]. Thus the use of terlipressin for variceal bleeding may prevent renal failure, which is frequently precipitated by variceal bleeding [187].

Somatostatin is empirically used as an initial bolus of 250 μg followed by a 250 μg/h infusion that is maintained until the achievement of a 24 h bleed-free period. The bolus injection can be repeated up to three times in the first hour if bleeding is uncontrolled. Therapy may be further maintained for up to 5 days to prevent early rebleeding [203]. Major side effects with somatostatin are rare. Minor side effects, such as nausea, vomiting and hyperglycemia occur in up 30% of patients [203–205]. Several randomised controlled trials showed that somatostatin significantly improves the rate of control of bleeding compared with placebo or non-active treatment, but mortality was not reduced [120,199]. Somatostatin has been compared with terlipressin and no differences were found for failure to control bleeding, rebleeding, mortality or in the incidence of adverse events in both treatment groups [120]. The use of higher doses (500 μg/h) causes a greater fall in HVPG and translates into increased clinical efficacy and lower mortality in the subset of patients with more difficult bleedings (those with active bleeding at emergency endoscopy) [205].

Octreotide is a somatostatin analogue with longer half-life. This, however, is not associated with longer hemodynamic effects [206]. The optimal doses are not well determined. It is usually given as an initial bolus of 50 μg, followed by an infusion of 25 or 50 μg/h [199]. As with somatostatin, therapy can be maintained for 5 days to prevent early rebleeding. The safety profile of octreotide is close to that of somatostatin. The efficacy of octreotide as a single therapy for variceal bleeding is controversial. No benefit from octreotide was found in the only trial using octreotide or placebo as initial treatment [207], which may be due to rapid development of tachyphylaxis [206]. However, RCT's using octreotide after of sclerotherapy have shown a significant benefit in terms of reducing early rebleeding [208]. It has been speculated that this may be related to its ability to prevent post-prandial increase in portal pressure [199]. Mortality, however, was not affected [120,208]. These results suggest that octreotide may improve the results of endoscopic therapy but has uncertain effects if used alone. When compared with other vasoactive drugs, octreotide was better than vasopressin and equivalent to terlipressin, again suggesting a clinical value from the use of octreotide, although all these studies were underpowered and none was double-blind [120].
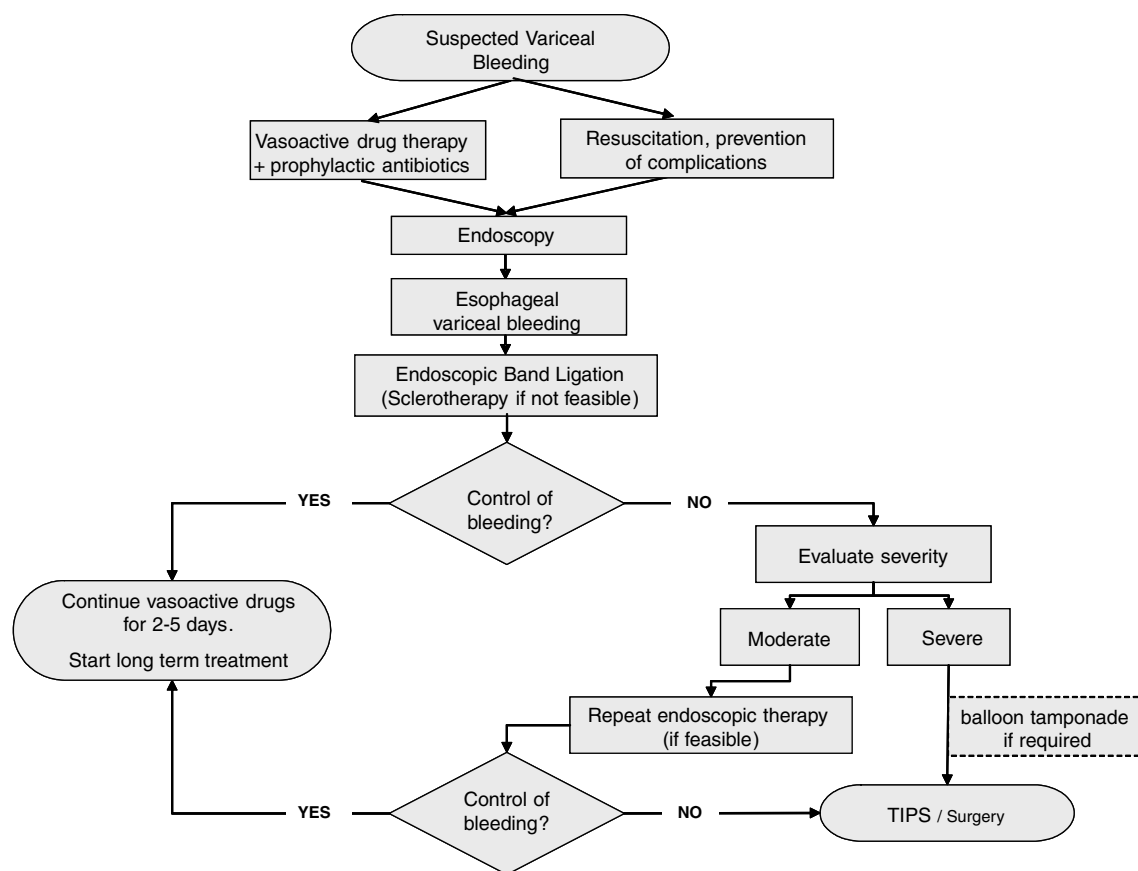
Fig. 4. Algorithm of the management of acute bleeding from ruptured oesophageal varices.

6.2.2.2. Endoscopic therapy. Both sclerotherapy and band ligation (EBL) have shown to be effective in the control of acute variceal bleeding. Two randomised trials specifically compared band ligation and sclerotherapy in acute variceal bleeding [209,210]. In one of them all patients received also pharmacological therapy (somatostatin) [210]. In eight additional trials these two modalities were compared both in acute bleeding and in the prevention of rebleeding. Meta-analysis shows that EBL is better than sclerotherapy in the initial control of bleeding, and is associated with less adverse events and improved mortality. Additionally, sclerotherapy, but not EBL, may increase portal pressure [211]. Therefore EBL is the endoscopic therapy of choice in acute variceal bleeding, though injection sclerotherapy is acceptable if band ligation is not available or technically difficult. Endoscopic therapy can be performed at the time of diagnostic endoscopy, early after admission, provided that a skilled endoscopist is available. This is important since there has been an increased frequency of aspiration pneumonia since emergency endoscopic therapy has become universal practice.

6.2.2.3. Current recommendations for initial treatment (Fig. 4). The current recommendation is to start vasoactive drug therapy early (ideally during the transferral or

to arrival to hospital, even if active bleeding is only suspected) and performing EBL (or injection sclerotherapy if band ligation is technically difficult) after initial resuscitation when the patient is stable and bleeding has ceased or slowed (Text Box 3). The rationale for this comes from a number of RCT's demonstrating that early administration of a vasoactive drug facilitates endoscopy and improves control of bleeding and 5-day rebleeding [198,204,212,213]. Vice versa, the association of endoscopic therapy also improves the efficacy of vasoactive treatment [204]. The optimal duration of drug therapy is not well established. Current recommendation is to maintain the drug for 2–5 days [70].

Text Box 3
Prevention of rebleeding: recommendations

- Patients with cirrhosis who survive a variceal bleeding episode have a very high risk of rebleeding (about 60% at 1-yr).
- All patients surviving a bleeding episode should receive specific therapy to prevent rebleeding.
- Non-selective beta-blockers ± ISMN, endoscopic band ligation (EBL) or both should be used for prevention of recurrent bleeding. Combination of beta-blockers ± ISMN and EBL may be the best treatment.

- In patients who bleed and were on beta-blockers for primary prophylaxis, EBL should be added to drug treatment. Similarly, in patients previously treated with EBL and with no contraindication to beta-blockers, propranolol or nadolol should be added to EBL.
- TIPS is very effective in the prevention of recurrent bleeding from oesophageal varices, and the efficacy is not significantly different from that of shunt surgery (distal splenorenal shunt or 8 mm H-graft shunt), especially since the introduction of PTFE-covered stents. However TIPS does not improve survival and therefore it should be only offered to patients who rebled from oesophageal or gastric varices despite optimal medical and/or endoscopic treatment.
- It is possible that high-risk patients may benefit from an early decision for TIPS, but this should be further evaluated.

6.2.3. Rescue therapies: tamponade, surgery and TIPS

In 10–20% of patients variceal bleeding is unresponsive to initial endoscopic and/or pharmacologic treatment. If bleeding is mild and the patient is stable a second endoscopic therapy might be attempted. If this fails, or bleeding is severe, the patient should be offered a derivative treatment, before his clinical status deteriorates further. Balloon tamponade achieves hemostasis in 60–90% of variceal bleedings [24] but should only be used in the case of a massive bleeding, for a short period of time (less than 24 h) as a temporal "bridge" until definite treatment is instituted. Bleeding recurs after deflation in over half of the cases and severe complications are common. A recent report suggests that the use of oesophageal covered stents might achieve hemostasis in most patients with refractory bleeding [72], with the advantage over tamponade of less severe complications despite longer periods of treatment. Adequately designed trials should confirm these findings.

Both TIPS and surgical shunts are extremely effective in controlling variceal bleeding (control rate approaches 95%), but due to worsening of liver function and encephalopathy mortality remains high [24,214]. TIPS is first choice, since most patients requiring rescue treatment have advanced liver disease with unacceptable surgical risk. Anyhow, rarely, if ever, a patient with a Child-Pugh score over 13 will survive TIPS. This clearly indicates that some patients do not benefit from TIPS in this setting, and sometimes it is difficult to make a clinical based decision. Prognostic scores [215] may provide objective parameters to ease the decision of not offering invasive treatments in difficult cases.

A recent randomised trial explored whether patients with poor prognostic indicators might benefit from a more aggressive therapeutic approach ab initio. Patients with high risk (with HVPG > 20 mm Hg) were randomised to receive standard therapy or TIPS. Those who underwent early TIPS had significantly less treatment failure and lower mortality than patients undergoing standard therapy [216]. An ongoing multicenter study will confirm whether early TIPS (performed with covered stents) is superior to combination therapy in high-risk patients (ISRCTN58150114).

6.3. Gastric varices

Gastric varices develop in approximately 20% of patients with portal hypertension [217]. They are the source of 5–10% of all upper digestive bleeding episodes in patients with cirrhosis. The risk of gastric variceal bleeding is lower than that of oesophageal variceal bleeding, but gastric variceal bleeding, in particular that from fundal varices, tends to be more severe, to require more transfusions, and to have a higher mortality rate [217]. Fundal varices account for 1–3% of variceal bleeds.

The optimal treatment of gastric fundal varices has not been determined, since there are few RCTs and most data come from retrospective series. The initial treatment is similar to that of oesophageal variceal bleeding, including the administration of a vasoactive drug (either terlipressin, somatostatin or a somatostatin analogue). Balloon tamponade, with the Linton-Nachlas tube, has been used with limited success [71,218], but may serve as a bridge to derivative treatments in massive bleedings.

Some endoscopic therapies are promising, but quality information is scarce, and most studies include both fundal varices and gastro-oesophageal varices. Sclerotherapy, variceal obturation with tissue adhesives ("glue injection"), thrombin, EBL and ligation with large detachable snares have been reported [219]. In most uncontrolled series cyanoacrylate has reported a high rate of control of bleeding (about 90%) [220]. Two recent randomised trials compared EBL with cyanoacrylate injection. In one trial cyanoacrylate injection was more effective and safer than EBL in the control of acute bleeding, and was associated with less rebleeding [176]. In another trial both treatments were equally effective controlling acute bleeding, but rebleeding was more frequent in the EBL group [178]. In another study, cyanoacrylate was better than sclerotherapy both in achieving initial hemostasis and in achieving faster variceal obliteration [177]. These trials suggest that cyanoacrylate injection is the most effective endoscopic therapy in acute bleeding from gastric fundal varices. This technique however needs expertise, and is usually not feasible during active bleeding.

TIPS is very effective in the treatment of bleeding gastric varices, with more than 90% success rate for initial hemostasis and very low rebleeding rate [221,222]. A

very recent trial has shown that it is more effective than glue injection in preventing rebleeding [223]. Derivative and devascularization surgery are also effective, but with limited applicability in advanced cirrhosis. Another approach is the retrograde intravascular obliteration of spontaneous splenorenal shunts that are frequently present in patients with large fundal varices [224]. To date, however, this treatment has not been tested in RCTs.

The authors' recommendation is to start treatment with a vasoactive drug. If bleeding is not controlled and if an expert endoscopist is available, variceal obturation might be attempted. In cases of massive bleeding or after failure of previous therapies, TIPS (or surgical shunt in Child A patients) is mandatory. A second attempt at endoscopic therapy should never be allowed in these patients.

6.4. Portal hypertensive gastropathy (PHG)

Portal hypertensive gastropathy is a macroscopic finding of a characteristic mosaic like pattern of the gastric mucosa ("mild" PHG), red-point lesions, cherry red spots, and/or black-brown spots ("severe" PHG) [225]. These lesions, however, are not entirely specific, i.e. can occur in the absence of portal hypertension. In PHG there is marked dilatation of the vasculature of the gastric mucosa and submucosa, together with an increased blood flow and tendency to decreased acid secretion. PHG is unrelated to *Helicobacter pylori* infection. The overall prevalence of PHG in patients with cirrhosis strongly correlates with the severity of the disease and ranges between 11% and 80% [225]. The incidence of acute bleeding is low (less than 3% at 3 years) with a mortality of 12.5%, while the incidence of chronic bleeding is 10–15% at 3 years. In acute bleeding from PHG beta-adrenergic blockers, somatostatin, octreotide, vassopressin, terlipressin and estrogens have been proposed based on their ability to decrease gastric perfusion in this condition [226–229]. However, only one uncontrolled study so far has evaluated one of these drugs (somatostatin) in acute bleeding from PHG [230]. Hemostasis was achieved in all patients. Non-selective beta-blockers effectively decrease chronic bleeding from PHG [231].

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