Variceal Hemorrhage

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I wish to dedicate this book to
my wife, Giuliana. She is my rock
and the love of my life.

Roberto de Franchis, MD, AGAF

This book is dedicated to all the
people who have supported
and encouraged me throughout
my personal and professional life.

Alessandra Dell'Era, MD, PhD

Preface

Portal hypertension is associated with the most severe and lethal complications of cirrhosis. Despite the progress achieved over the last decades, the 6-week mortality associated with variceal bleeding is still on the order of 10–20 %. Awareness of the problems concerning the management of variceal hemorrhage has stimulated the organization of a series of international workshops aimed at assessing the evidence and issuing recommendations concerning the diagnosis, the prevention, and the treatment of this severe medical emergency. The most recent of these workshops took place in Baveno, Italy, in the spring of 2010 (Baveno V). In Baveno V, the recommendations were updated to incorporate the scientific evidence accumulated over the preceding 5 years; however, several "grey areas" remained, and some of them have been addressed in studies published after Baveno V.

This book is aimed at updating the scientific evidence concerning several aspects of variceal hemorrhage, including the natural history, the diagnosis of esophageal varices, the assessment of the risk of bleeding, and the identification of high risk groups and of patients who may benefit or may be harmed from different treatments. The different steps in the management of acute variceal bleeding are also critically analyzed. We managed to enlist some of the most prominent world experts in the different areas, who contributed their best in their areas of expertise.

This book is aimed at serving as a useful reference for physicians and researchers dealing with and interested in the different aspects of this challenging clinical situation.

We hope you enjoy this text as much as we enjoyed helping create it.

Milan, Italy

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Part I
Pathophysiology, Natural History, Stages, and Diagnosis

Chapter 1
Pathophysiology of Portal Hypertension

Yasuko Iwakiri and Roberto J. Groszmann

Introduction

It is the aim of this section on pathophysiology to provide an overview of current thinking about the circulatory derangements observed in portal hypertension. An understanding of this pathophysiology gives us a framework for understanding existing pharmacologic therapies for portal hypertension and for devising rational investigational strategies.

In order to provide a simplified and clear idea of the pathogenesis of portal hypertension, we like to present it, using Ohm's law that states that changes in pressure ($P1-P2$) along a blood vessel are a function of the interplay between blood flow (Q) and the resistance (R) that the vascular bed offers to that flow.

$$P1-P2=Q\times R.$$

The pathophysiology of portal hypertension is best approached by analyzing these components separately, although mathematical formulas necessarily oversimplify the complex and dynamic interactions that exist in biologic systems. Unlike pressure and flow, resistance cannot be directly measured, but it can be derived from pressure and flow. Resistance to the flow of blood in vessels is best understood when expressed according to Pouseuille's Law:

$$\frac{R=8nL}{\pi r^4}$$

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in which: n = coefficient of viscosity
L = length of vessel
r = radius of vessel

Expressed in these terms, substitution of resistance (R) into Ohm's equation yields:

$$\frac{P1 - P2 = Q\left(8nL\right)}{\pi r^4}$$

Under physiologic conditions, resistance is mainly a function of changes in r, which have a dramatic influence because these are taken to the fourth power. In contrast, L and n are basically constant because neither the length of a vessel nor the viscosity of blood varies greatly under usual circumstances.

The liver is the main site of resistance to portal blood flow. The normal liver may be conceptualized as a huge and distensible vascular network with very low resistance. The liver itself has no active role in regulating portal inflow; this function is provided by vascular resistance at the splanchnic arteriolar level. Hence, the liver is a passive recipient of fluctuating amounts of blood flow, which it accommodates by capillary (sinusoidal) recruitment when flow increases, as in postprandial hyperemia. A normal liver can encompass a wide range of portal blood flow with minimal effect on pressure in the portal system.

Hepatic Vascular Resistance: Structural

The structural changes in the intrahepatic vasculature associated with liver fibrosis/cirrhosis are the most important factor involved in the increased intrahepatic resistance. This section summarizes morphological changes in the intrahepatic vasculature of diseased livers with different etiologies as well as those in liver sinusoidal endothelial cells (LSECs) (Fig. 1.1).

Historical Observations

Early studies of the hepatic vascular system in portal hypertensive states contributed greatly to our understanding of vascular resistance in the pathophysiology of portal hypertension. In McIndoe's 1928 study of corrosion casts of the vascular system in cirrhotic livers, changes in the portohepatic system are vividly described:

> One of the most superficially obvious changes is the marked diminution in the total hepatic vascular bed. The main trunks are attenuated and irregularly stenosed, having lost that appearance of robust strength so notable in the normal vessels. Their larger branches are given off at unusually abrupt angles and occasionally show irregular deviation to one side or the other as though pushed or pulled by an invisible force. It is among the finer branches, however, that the more profound alterations are to be seen. The tiny portal veins are distorted

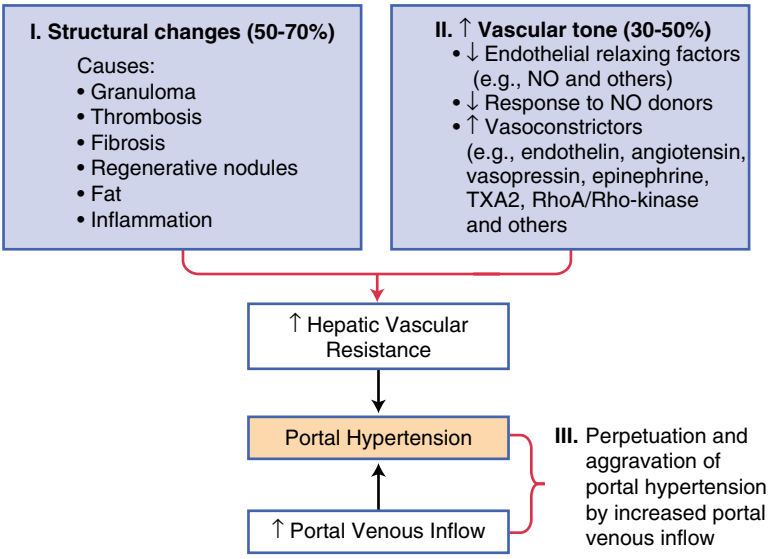

Fig. 1.1 The factors involved in the development and maintenance of portal hypertension. I. Structural increases in vascular resistance induced by factors listed under structural changes. II. Increased vascular tone induced by a reduction in the availability of endothelial relaxing factors, decreased response to nitric oxide (NO), and increased response of the intrahepatic circulation to local and systemic vasoconstrictors. III. Perpetuation and aggravation of portal hypertension by hyperdynamic splanchnic circulation. *TXA2* thromboxanA2

> beyond belief, twisted and curled on themselves, and finally broken up into a network of stunted venules from which irregularly scattered terminals arise. In the tree of the hepatic vein, the same change is found. It is usually difficult to detect any normal central veins, especially if the cirrhosis is far advanced. [1]

These gross morphological aberrations in the portal and hepatic venous systems gave rise to the conception of portal hypertension as a vascular obliterative process in which fibrous tissue and regenerative nodules were responsible for increased resistance to the flow of blood [2].

Anatomical Site of Increased Resistance to Portal Blood Flow

The site of increased resistance to portal blood flow is easily defined in prehepatic portal hypertensive states such as splenic or portal vein obstruction. Likewise, in the uncommon syndrome of inferior vena cava web or in congestive heart failure, the posthepatic locus of obstruction is readily defined. The situation is far more complex in intrahepatic forms of portal hypertension. In these diseases, there are few pure presinusoidal, sinusoidal, or postsinusoidal lesions. For example, alcoholic liver disease is a heterogeneous collection of disorders with postsinusoidal and

sinusoidal areas of obstruction to blood flow. Likewise, hepatic schistosomiasis is often defined as a presinusoidal disease, with granulomas developing in portal areas in response to the presence of parasite eggs [3]. However, in end-stage schistosomiasis, there may also be an elevation in the wedged hepatic venous pressure, reflecting an increase in resistance in the sinusoids and correlated histologically with collagen deposition in the space of Disse and sinusoidal narrowing [4].

Capillarization of Sinusoidal Endothelial Cells in Cirrhotic Livers

Deposition of collagen in the space of Disse and capillarization of hepatic sinusoids are characteristic lesions observed in all types of cirrhosis. Electron microscopic examination of biopsy specimens reveals an increase in the amount of collagen in the perisinusoidal space, which normally contains little or no collagen. This may progress to formation of a basement membrane in the Disse space, resulting not only in impairment of exchange of nutrients and oxygen between hepatocyte and sinusoid, but also in physical encroachment on the sinusoid due to widening of the Disse space, with consequent increase in sinusoidal vascular resistance. Capillarization is a term introduced by Schaffner and Popper [5] to describe the dramatic change in the hepatic microcirculation in which the sinusoids evolve from highly permeable capillaries to impermeable membranes which become barriers to the transfer of important metabolic and nutrient products which are necessary for normal liver function. Capillarization of the sinusoids may also increase vascular resistance by impairing lymphatic drainage and causing widening of the Disse space due to edema.

Hepatic Vascular Resistance: Functional

The morphological changes occurring in chronic liver diseases are undoubtedly the most important factor involved in the increased intrahepatic resistance. However, recent data also demonstrate a role of functional factors that lead to increased vascular tone, similar to what is seen in the arterial hypertension. Hepatic cells that play important roles in the regulation of intrahepatic vascular resistance include hepatic stellate cells (HSCs) and LSECs. This section discusses how these cells contribute to increased intrahepatic vascular resistance in cirrhotic livers.

Hepatic Stellate Cells

In chronic liver disease and also during acute liver injury, HSCs acquire contractile properties and contribute to the dynamic modulation of intrahepatic resistance. These cells may act as pericytes, a type of cell, which has been shown to regulate

blood flow in other organs. HSCs, which are also the main source of collagen synthesis in chronic liver diseases, may contribute to the regulation of hepatic blood flow at the microcirculatory level. HSCs are strategically located in the sinusoids with perisinusoidal and interhepatocellular branching processes that contain actin-like filaments. They also express the alpha smooth muscle actin gene, which is characteristic of vascular smooth muscle cells. The characteristics of these cells make them similar to myofibroblasts. Myofibroblasts are intermediate in structure between smooth muscle cells and fibroblasts. Myofibroblast-like cells have been shown to exist in fibrous septa around the sinusoids and terminal hepatic venules in cirrhotic livers. These cells are postulated to play a role in the regulation of vascular resistance in the cirrhotic liver [6].

Liver Sinusoidal Endothelial Cells

LSECs play important roles in the regulation of intrahepatic vascular tone by releasing various vasoactive substances [7–11]. Vasoactive substances released from LSECs diffuse to HSCs and cause their relaxation or constriction. HSC contraction is triggered by endothelin-1 (ET-1), Substance P, angiotensin II, norepinephrine, prostaglandin F2, thromboxane A2 (TXA2), and thrombin. Relaxation of HSCs can be induced by acetylcholine, vasointestinal peptide, nitric oxide (NO), carbon monoxide, prostaglandin E2, and adrenomedullin [10, 12]. Among these vasoactive agents, ET-1 and NO are known to play central roles in intrahepatic vascular resistance in the sinusoidal microcirculation. ET-1 has dual vasoactive effects. ET-1 induces HSC contraction by binding to endothelin A (ETA) receptors located on HSCs [6], while it causes vasodilation by binding to endothelin B (ETB) receptors on LSECs, which stimulates endothelial nitric oxide synthase (eNOS) activity through the activation of protein kinase B/Akt [7, 9–11, 13].

Phosphorylations of Akt and eNOS are significantly impaired in cirrhotic liver [14]. It was shown that ET_B receptor-mediated vasodilation is through Akt phosphorylation and subsequent phosphorylation (activation) of eNOS via G-protein- coupled receptor signaling, specifically G-protein βγ [15]. Furthermore, it was shown that G-protein-coupled receptor kinase-2 (GRK2), an inhibitor of G-protein- coupled receptor signaling, is up-regulated in LSECs in cirrhotic liver, which impairs Akt phosphorylation and NO production. Thus, GRK2 knockdown restores Akt phosphorylation and NO production, which then improves portal hypertension [16]. Increased vascular tone seen in cirrhotic livers is due to a deficit of endothelial vasodilators or an increase in vasocontrictors, but mainly by a combination of both.

Besides NO and ET-1, TXA2 production in LSECs contributes to the increased intrahepatic resistance in cirrhotic livers through HSC contraction, which is due to increased cyclooxygenase (COX)-1 levels, not COX-2, in LSECs [17]. It was shown that impaired response to acetylcholine in cirrhotic livers is associated with an increased production of TXA2, which is completely prevented by COX-1 selective blockers and by TXA2 antagonists. This finding suggests that an increased

production of a COX-1-derived vasoconstrictor prostanoid TXA2 is at least in part responsible for HSC contraction and a subsequent increase in intrahepatic vascular resistance [18].

Factors Leading to LSEC Dysfunction

LSECs, being the first defense of the intrahepatic circulation, are prone to receive a wide range of insults, such as oxidative stress, inflammation, and alcohol, during the liver injury.

Oxidative Stress

Reactive oxygen species (ROS) directly react with NO and decrease the bioavailability of NO in endothelial cells [19, 20], leading to LSEC dysfunction. Thus, treatment with an antioxidant, such as vitamin C, could ameliorate LSEC dysfunction [21–24]. One study demonstrated that ascorbic acid (i.e., vitamin C) treatment in cirrhotic patients significantly improved LSEC functions, as indicated by improved flow-dependent vasodilation, which could partly be due to decreased oxidative stress in the intrahepatic circulation [25]. Those patients had significantly decreased plasma levels of ascorbic acid and increased oxidative stress as indicated by increased plasma levels of malondialdehyde (MDA, a marker of lipid peroxidation, thereby an indicator of oxidative stress). Administration of ascorbic acid to these patients significantly decreased MDA levels and attenuated the postprandial increase in the hepatic venous pressure gradient. These observations suggest that antioxidant treatment, at least in part, corrects LSEC dysfunction observed in cirrhotic patients, possibly by increasing the bioavailability of NO in the intrahepatic circulation [25].

Oxidative stress not only decreases NO bioavailability but also decreases NO production by impairing eNOS activity in LSECs [21] by two ways. One way is to increase an interaction of eNOS with caveolin-1 (inhibitory for eNOS activity). The other is by decreasing the eNOS interaction with ET_B receptors, which is known to stimulate eNOS activity. Furthermore, oxidative stress inhibits ET-1 induction of eNOS phosphorylation at Ser1177 site (an active site of eNOS) in LSECs [21].

Inflammation

Inflammation in cirrhosis also causes LSEC dysfunction by reducing eNOS activity. For example, elevated endotoxin in cirrhotic livers increases caveolin-1 expression as well as an interaction between caveolin-1 and eNOS, leading to the inhibition of eNOS activity. Endotoxin also suppresses ET-1-induced eNOS phosphorylation at Ser1177 site, but increases it at Thr495 (an inhibitory site of eNOS), leading to further inhibition of eNOS activation [26, 27].

Alcohol

Metabolic products of alcohol metabolism, such as acetaldehyde and MDA, bind to proteins and form stable adducts, which have been known to cause many deleterious effects on various cells in the liver, including LSECs. These adducts are associated with the pathogenesis of fibrosis by inducing the expression of fibronectin in SECs [28] and thereby leading to the activation of HSCs and the production of type IV collagen [29]. Alcohol injection also induces superoxide radical generation in the liver and contributes to LSEC dysfunction [30, 31].

The Flow Factor: Hyperdynamic Circulation

If blood flow in the portal system were fixed in the face of increased resistance, then Ohm's law ($P1-P2=Q\times R$) would mandate an increase in portal pressure. This is the basis for the backward flow theory of portal hypertension, which postulates that the driving force for elevation of portal pressure is increased portal vascular resistance [32].

In reality, while liver perfusion with portal blood is decreased in portal hypertension, blood flow entering the portal system is actually greatly increased by an increment made up of blood which bypasses the liver in porto-systemic shunts. There is a marked increase in splanchnic blood flow with much of this flow shunted around the liver through portal-systemic collaterals [33, 34]. This hyperdynamic splanchnic circulation, or more simply the hyperdynamic circulation, has a role in elevating portal pressure and is a factor in the maintenance of portal hypertension, even in the presence of an enormous collateral vascular bed. The hyperdynamic circulation is observed in humans and laboratory animals with portal hypertension. This circulatory state is characterized by decreased arteriolar resistance, resulting from peripheral vasodilation in many regional vascular beds, including the splanchnic renal and skeletal muscle circulations [33]. Vasodilation is accompanied by increased cardiac index and regional blood flows [33]. Hyperkinetic blood flow is present in the splanchnic as well as the systemic circulation with flow to the intestines, stomach, spleen, and pancreas increased by approximately 50 % above control values. The hyperdynamic circulation is manifested in patients with warm, well-perfused extremities, bounding pulses and rapid heart rates, as well as a high cardiac index and expanded blood volume.

We believe that the initial vasodilation occurs in the splanchnic circulation and that the heart response is directly related to a combination of splanchnic vasodilation and expansion of the plasma volume together with an increased venous return to the heart, in large part, through portal-systemic shunts. Although vasodilation is essential as the initiating factor, there is no hyperdynamic circulation without expansion of the plasma volume and portal-systemic shunting [35, 36]. Studies in rats with portal vein stenosis point to a role for plasma volume expansion in the development of the hyperdynamic circulation [35]. Chronic dietary sodium restriction hinders the expansion

of the plasma volume, and, in turn, blunts the expression of the hyperdynamic syndrome [35]. In this case, marked reductions in systemic and splanchnic blood flow are observed with resulting reduction in portal pressure, underscoring the importance of hyperdynamic splanchnic blood flow in maintaining portal hypertension in this experimental model. Moreover, a reduction in plasma volume by introduction of dietary sodium restriction at the height of the hyperdynamic circulation demonstrates that systemic and splanchnic hyperemia, together with portal pressure elevation, are partially reversible. Furthermore, in the long run, the heart behaves as it does in other forms of high cardiac output syndrome: initial compensation according to the degree of individual cardiac reserve, followed sooner or later by some degree of heart failure. The cardiac index is usually higher than normal (>4L/min/m^2). It is obviously insufficient to maintain arterial pressure on the face of progressive vasodilation. Interestingly, high cardiac output failure is reversible once the initial cause leading to the high cardiac output is treated. This reversal has also been observed in patients with cirrhosis after liver transplantation [37].

Arterial Vasodilation

A wide variety of vasodilator molecules play an important role in arterial vasodilation in the splanchnic and systemic circulations in portal hypertension. Several important vasodilator molecules are summarized next.

Nitric Oxide (NO)

NO has been recognized as the most important vasodilator molecule in arterial vasodilation observed in the splanchnic and systemic circulations of cirrhotic patients and animal models of portal hypertension. Using a surgical model of portal hypertension, partial ligation of portal vein (PVL), the relationship between portal pressure and the development of the hyperdynamic circulation was studied [38]. The degree of portal pressure is significantly associated with the severity of the hyperdynamic circulation [38]. Furthermore, different degrees of portal pressure trigger eNOS activation in the different parts of the splanchnic circulation and with distinct molecular mechanisms [38]. For example, a mild increase in portal pressure, probably more relevant to the gradual development of portal hypertension in cirrhosis, increases vascular endothelial growth factor (VEGF) expression and eNOS phosphorylation at Ser1176 (rat) in the intestinal microcirculation in rats, which is reversed by the administration of VEGF receptor-2 blocker [38].

In contrast, an induction of eNOS activity in the arteries of the splanchnic circulation requires higher portal pressure than that in the intestinal microcirculation. The underlying mechanism is that an acute and higher portal pressure induces vasoconstriction first in the arterial splanchnic circulation due to a myogenic reflex caused by a sudden increase in portal pressure. This initial vasoconstriction then

triggers phosphorylation and activation of eNOS through Akt/protein kinase B activation, leading to increased NO production and vasodilation in the arteries of the splanchnic circulation [39, 40]. Activation of Akt might be due to an increase in shear stress induced by this myogenic reflex and vasoconstriction, although other mechanisms may be involved [41]. These observations clearly indicate that portal pressure is an important factor that regulates an induction of vasodilation in the different parts of the splanchnic circulation [38].

Vascular Endothelial Growth Factor

An increase in portal pressure stimulates the secretion of VEGF that contributes to neoformation of porto-systemic collateral. Besides this angiogenic capacity, VEGF can cause vasodilation by stimulating eNOS activity. Upon binding to its receptor on endothelial cells, VEGF induces signaling cascades to activate Akt and subsequently activate eNOS through phosphorylation at Serine 1177 (human). An administration of VEGF receptor-2 blocker (SU5416) significantly reduces porto-systemic collateral formation and decreases portal pressure in portal hypertensive rats [42]. Blocking the VEGF signaling could be a beneficial therapeutic strategy for the treatment of hyperdynamic circulation in cirrhosis with portal hypertension [43].

Carbon Monoxide

Studies showed that CO, an end product of the heme oxygenase (HO) pathway, is also involved in arterial vasodilation in portal hypertensive rats [41, 44–48]. HO is an enzyme that catabolizes heme derived from heme-containing proteins, especially hemoglobin to biliverdin, which is then rapidly transformed to bilirubin and CO. CO causes vasodilation through activation of guanylate cyclase of vascular smooth muscle cells [49]. Under pathologic conditions, HO activity increases markedly via an induction of an inducible isoform of the enzyme, HO-1, also known as heat shock protein 32 [50]. In portal hypertension, HO-1, not HO-2, is up-regulated in the systemic and splanchnic arterial circulations. CO, synergistically with NO, plays a role in arterial vasodilation observed in cirrhosis with portal hypertension [41, 44, 45, 47, 48].

Anandamide (Arachidonyl Ethanolamide)

Anandamide is one of the endogenous lipid ligands endocannabinoids and causes hypotension through its binding to CB1 receptors [51]. In cirrhosis, it is shown that the activation of CB1 receptors within the mesenteric vasculature is associated with the development of splanchnic vasodilation. It is not clarified whether the vasodilatory effect of CB1 receptor activation is NO-dependent [10, 52, 53].

Conclusion

The study of portal hypertension is extremely important and urgent, given that effective treatments are limited to the end stage of cirrhotic patients. There is no doubt that knowledge in this area will continue to grow in basic science as well as the clinical arena, including studies in the experimental models that have given us a unique opportunity to provide a molecular basis for pathophysiological findings.

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Chapter 2
Natural History and Stages of Cirrhosis

Gennaro D'Amico

Introduction

The natural history of cirrhosis is characterized by an asymptomatic phase, referred to as "compensated cirrhosis," followed by a progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, designated "decompensated cirrhosis." In the compensated phase portal pressure may be normal or below the threshold of clinically significant portal hypertension [1] although esophageal varices may appear still in the compensated phase of the disease. Decompensation is defined by the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy, or jaundice [2]. Progression of the decompensated disease may be accelerated by the development of other complications such as (re)bleeding, renal impairment [refractory ascites, hepatorenal syndrome (HRS)], hepatopulmonary syndrome, and sepsis [spontaneous bacterial peritonitis (SBP)]. The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage.

This chapter summarizes the major steps in the progression of cirrhosis through the compensated and the decompensated phases of the disease, and its prognostic indicators.

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Clinical Course of Compensated Cirrhosis

When cirrhosis is first diagnosed about a half of the patients are still in the compensated phase of the disease [3]. Median survival of patients with compensated cirrhosis has been reported as long as 10–12 years with death occurring mostly after transition into the decompensated disease. The reported median proportion of patients surviving at 1 and 2 years after the diagnosis of compensated cirrhosis is, respectively, 95 % and 90 % [3]. Development of esophageal varices and of decompensation are the major clinical events in this phase of the disease [4], mainly dependent on the progression of fibrosis and portal hypertension.

Progression of Fibrosis and Histological Stages of Cirrhosis

Accumulation of fibrosis occurs slowly along the course of the disease. It is a silent process related to the inflammatory activity of the underlying disease. Based on Laennec's cirrhosis classification, three histological stages of cirrhosis have been described and a modification of the Metavir stage 4 of fibrosis has been proposed as stages 4A, 4B, and 4C [5]. This histological staging system is based on thickness of fibrous bands and nodules size: the more thin the fibrous bands and the larger the nodules, the lower is the histological stage. Histological stages are also significantly related to the severity of portal hypertension and to the clinical severity of cirrhosis [6–8]. Several noninvasive tests to measure the amount of fibrosis are now available; liver stiffness (transient elastography, Fibroscan) is increasingly used in clinical practice particularly to rule out significant fibrosis or to rule in cirrhosis [9]. Liver stiffness significantly increases from stage 4A to 4C [8].

Development and Clinical Impact of Esophageal Varices

The median prevalence of varices in prognostic studies of cirrhosis including patients with compensated cirrhosis is 44 % while in those including decompensated patients it is 73 % [3]. Large cohort studies [10–12] have shown that the incidence of esophageal varices in patients with newly diagnosed cirrhosis is in the range of 5–8 % per year.

Varices do not develop below the threshold HVPG value of 10 mmHg [13, 14]. Above this threshold, the median time to development of varices and/or bleeding or other complications of portal hypertension is about 4 years [10]. Once developed, varices increase in size at a cumulative rate of approximately 5–7 % per year [11, 12]. Increase or reduction of HVPG is associated with corresponding variations of the risk of developing varices or of variceal size [10, 14, 15]. Thus, HVPG plays a key role both in development and progression of varices.

Table 2.1 Five-year survival in patients with compensated cirrhosis, respectively, without or with esophageal varices

Author (ref.)	Year	Patients (*n*)	5-Year survival %		Risk ratio	*p*
			No varices	Varices		
Merli [12]	2003	206	8	17	2.1	<0.05
D'Amico [3]	2006	806	6	13	2.1	<0.001
Bruno [4]	2009	327	2	9	4.5	<0.001
D'Amico [16]	2010	739	4	9	2.3	<0.0001
Zipprich [17]	2012	120	10	25	2.5	0.019
Vilar [18]	2013	402	3	8	2.6	<0.0001

Increasing size of esophageal varices is associated with increasing risk of bleeding (fourfold from absent to small varices and two- to threefold from small to large varices), of developing ascites, and of death.

Five-year mortality ranges from 2 to 10 % in patients with compensated cirrhosis without esophageal varices, while it ranges from 8 to 25 % year, after the development of varices [3, 4, 12, 16–18] (Table 2.1).

Decompensation

Overall, decompensation occurs at a fairly constant rate of 5 % per year [19, 20]. The risk of decompensation has been reported to be approximately double in patients with esophagogastric varices compared to patients without varices [3, 4, 18]. Other reported prognostic indicators of decompensation, although not yet validated, are the model for end stage liver disease (MELD) [21], albumin, hepatic vein pressure gradient ≥10 mmHg [22], and increased body mass index (BMI) [23]. Ascites is the most frequent decompensating event, followed by bleeding, jaundice, and encephalopathy [19, 20]. It is to note that jaundice and encephalopathy are rarely the first decompensating event, occurring mainly after ascites or bleeding [16]. Decompensation is associated with expected 1- and 2-year survival rate of approximately 60 % and 45 %, respectively, compared with 95 % and 90 % in compensated cirrhosis [3].

Mortality

Mortality in patients with compensated cirrhosis is low, in the order of 1–3 % per year and it is significantly higher in patients with than without esophagogastric varices (Table 2.1). It is caused by a decompensating event or by a liver-related event in approximately half of patients dying while compensated: most frequently bleeding, HRS, or liver failure precipitated by sepsis, bleeding, or other acute clinical events.

In the remaining cases, death is usually caused by non-liver-related causes [4, 18]. Although death is the most important event in whichever disease stage, it is clearly a rare event in compensated cirrhosis, particularly when it is not linked to a decompensating event. Competing risks analysis of the clinical course of the disease has shown that death occurs very rarely before the development of esophagogastric varices or of decompensation. Both these events herald disease progression and increased risk of death. It is therefore at the prevention of these events that clinical research should aim to improve survival of compensated cirrhosis.

Clinical Course of Decompensated Cirrhosis

The appearance of ascites, variceal bleeding, encephalopathy, or jaundice, the major clinical manifestations of liver cirrhosis, marks the transition from the *compensated* phase into the *decompensated* phase of cirrhosis [19, 20, 24].

Ascites and Related Complications

Ascites develops when HVPG has increased above 10–12 mmHg. When cirrhosis is first diagnosed, the prevalence of ascites ranges from 20 to 60 % according to the referral pattern [3]. The incidence of ascites in compensated cirrhosis is about 5 % per year [19, 20]. Median survival after the appearance of ascites was reported in the order of approximately 2 years in the 1980s [19, 20, 24] while it approaches 4 years in the 2000s [25]. Therefore, although the outcome of patients with ascites has much improved in the last 2–3 decades, mortality after development of ascites is still high. The clinical course of patients with ascites is characterized by several events which markedly affect the expected survival. Refractory ascites, SBP, and HRS are the most relevant.

Refractory ascites is defined as ascites that cannot be mobilized or which recurs early after paracentesis because of a lack of response to sodium restriction and diuretic treatment, provided that criteria for diuretic treatment have been fulfilled. Refractory ascites occurs in approximately 5–10 % of patients with ascites [25, 26]: the incidence is approximately 2–4 % per year following the first episode of ascites [25]. When refractory ascites is established, the expected 1-year survival is in the order of 36–50 % [25, 27]; transjugular intrahepatic portacaval shunt (TIPS) may increase this figure up to approximately 60 % particularly in patients with bilirubin <3 mg, serum sodium ≥130 mEq/L, and age <60 [28]. Prognostic indicators of development of refractory ascites are Child-Pugh [29] score >8 and hepatitis C virus (HCV) infection, while indicators of poorer survival in patients with refractory ascites are low protein level in the ascitic fluid, higher Child-Pugh score, previous SBP, and history of heavy alcohol consumption (>80 g/day in men and >40 g in women) [30].

SBP is among the most frequent infections in patients with cirrhosis, representing 25 % of all infections in these patients. The incidence may be as high as 65 % in 1 year in high risk patients with borderline renal function, ascitic fluid protein level ≤1.5 g/dL, and Child-Pugh score ≥9 with bilirubin ≥3 mg/dL [31]. Median 1- and 12-month mortality following an episode of SBP is 32 % and 66 %, respectively [32]. Early diagnosis and prompt antibiotic treatment allow 30-day survival of 80 % [33], compared with the 0 % reported in the 1960s when SBP was first described [34]. However, failure of initial treatment occurs in 10 % of patients and is associated with 30-day survival of 30–50 %. Following a first episode of SBP the 1-year probability of a recurrent episode is 70 % [33] and corresponding survival is 50–80 % [35, 36]. Daily quinolone prophylaxis reduces the recurrence rate to approximately 20–25 % [37].

HRS is a functional renal failure defined by creatinine >1.5 mg/dL, no beneficial effect of plasma expansion, the absence of shock, exclusion of recent use of nephrotoxic drugs, and exclusion of parenchymal kidney disease [36]. Type-1 HRS consists of a severe and rapidly progressive renal failure with doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks. Bacterial infections, gastrointestinal hemorrhage, major surgical procedures, or acute-on-chronic liver failure (ACLF) are the most frequent precipitating events. Type-2 HRS is a moderate renal failure with serum creatinine ranging from 1.2 to 2.5 mg/dL with a steady, slowly progressive course. The overall incidence of HRS (type-1 and type-2) was reported 39 % over 5 years in the 1990s [36] while in a recent study it was approximately 15 % over a similar time period [25]. In patients with refractory ascites it may be as high as 53 % in 1 year [38]. In type-1 HRS, hospital survival is less than 10 % and the expected median survival time only 2 weeks while patients with type-2 have a much longer median survival time in the order of 6 months [39].

Variceal Bleeding

The overall incidence of variceal bleeding is approximately 5 % per year in patients unselected for the presence of varices. The corresponding figure is 1–2 % in patients without varices at a previous endoscopy, 5 % with small varices, and 15 % with medium or large varices [40, 41].

Besides variceal size, major indicators of the bleeding risk are the Child-Pugh class, ascites, and red weal marks (newly formed vessels on the variceal wall) on endoscopy. The NIEC index [42] combines these risk indicators in a score which enable to identify patients with predicted 1-year bleeding risk from 6 to 76 %.

Variceal bleeding does not occur if HVPG is lower than 12 mmHg [13, 14] and the bleeding risk is virtually abolished if HVPG is reduced to levels below this threshold and it is significantly reduced if HVPG is reduced of ≥20 % from baseline [43].

The cause of upper gastrointestinal bleeding is ruptured esophageal varices in 60–70 % of all episodes in cirrhosis [44]. A rebleeding episode is separated from the index bleeding by at least a 24-h bleeding-free period [45, 46].

Variceal bleeding ceases spontaneously in 40–50 % of patients and treatment achieves control of bleeding within 24 h from admission in nearly 85 %. Immediate mortality from uncontrolled bleeding is approximately 5 % [44]. Prognostic indicators of failure to control bleeding are active bleeding on endoscopy, bacterial infection, and HVPG >20 mmHg. Six-week rebleeding is 20 % [44] and its risk indicators are active bleeding at emergency endoscopy, gastric varices, low albumin, high blood urea nitrogen, and HVPG >20. A simple prognostic score based on Child-Pugh score, systolic blood pressure, and nonalcoholic etiology has been recently shown to have similar predictive accuracy for 5-day treatment failure as HVPG in patients treated with pharmacologic and endoscopic therapy [47], suggesting that measurement of HVPG is not needed for early prognostic stratification in patients bleeding from esophageal varices.

Six-week mortality after variceal bleeding is 10–15 % with nearly a half of deaths caused by bleeding or early rebleeding and a quarter occurring in the first 5 days. Albumin, bilirubin, creatinine, encephalopathy, HCC, the number of transfused blood units, bacterial infection, and HVPG >20 mmHg are indicators of the risk of mortality within 6 weeks.

Following a first episode of variceal bleeding 1-year mortality is in the range of 30–60 % [48, 49], although early TIPS in selected patients at high risk of death may reduce this figure to 16 % [50]. Rebleeding occurs within 1–2 years in approximately 60 % of untreated patients and 30 % of those given treatments for the prevention of rebleeding [48, 49]. Reduction of HVPG to below 12 mmHg totally prevents recurrent bleeding [43].

Encephalopathy and Jaundice

The incidence of encephalopathy is approximately 2–3 % per year [19]; however, in the absence of ascites or previous bleeding it is even lower. Jaundice behaves similarly to encephalopathy with a low incidence in the range of 2–3 % per year [19] and almost always it occurs in patients with other severe manifestations of advanced cirrhosis [20]. When encephalopathy occurs in patients without ascites it is often related to a spontaneous portacaval or spleno-renal shunt. Median survival after appearance of jaundice or encephalopathy is 1–2 years (D'Amico, unpublished observations from references [11] and [20]). Therefore, the most important markers of decompensated cirrhosis are bleeding and ascites, while encephalopathy and jaundice are seldom the first decompensating event.

Sepsis

Bacterial infections may occur along the whole course of cirrhosis but they are far more frequent in patients with ascites. Bacterial translocation has been postulated as the main mechanism in the pathogenesis of spontaneous infections in cirrhosis,

as well as the hyperdynamic circulation which is a key factor in portal hypertension, ascites, and HRS. Approximately 30 % of infections are community-acquired, 30 % are health care-associated, and 35–40 % are nosocomial [51]. Clinical risk factors include poor liver function, variceal bleeding, low protein ascites, previous SBP, and hospitalization [51]. Moreover, in patients with variceal bleeding, bacterial infection is significantly associated with increased risk of failure of treatment in controlling the acute bleeding, as well as with increased risk of rebleeding and death. For this reason a specific recommendation to treat any cirrhotic patient with gastrointestinal bleeding for the prevention of bacterial infection has been made [52]. In a systematic review of studies reporting on the outcome of sepsis in cirrhosis, the median prevalence of ascites in patients with infections was 100 % (range 6.3–100 %) [32]. The most frequent infections are SBP (≈25 %), urinary tract infections (≈20 %), pulmonary infections (≈15 %), and bacteremia (12 %) [32]. Mean 1-year mortality following an episode of infection is 58.6 % [32].

Hepatocellular Carcinoma

Patients with cirrhosis are at high risk of developing HCC. In fact 70–90 % of HCC occur in patients with chronic liver disease or cirrhosis. Globally, HCV and hepatitis B virus (HBV) chronic infections are the most frequent risk factors for HCC in cirrhosis. The incidence is different according to the geographical area. In Europe and the USA the 5-year incidence of HCC in patients with HCV-related cirrhosis is about 17 % and it is 15 % in patients with HBV-related cirrhosis [53]. Other factors associated with the occurrence of HCC in cirrhosis are older age (>55 years), male sex, elevated α-fetoprotein (>20 ng/mL), and obesity [54, 55]. More recently esophageal varices have also been reported to be significantly associated with the development of HCC in cirrhotic patients with HCV-related cirrhosis [56].

Survival in patients with HCC and cirrhosis depends on the severity of the underlying disease and on the degree of portal hypertension [57–59]. In fact, median survival in patients with HCC and esophageal varices is in the order of 24 months and in those without varices is about 36 months [60]. Overall, these considerations indicate that HCC is a major clinical event in the course of cirrhosis, which may occur in any disease stage and, whenever occurs, it invariably determines a significant reduction of survival.

Disease Stages

The typical representation of cumulative survival by Kaplan–Meier curves does not account for the real clinical course of patients with a definite clinical characteristic or disease stage. For example, a survival curve of patients with compensated cirrhosis at diagnosis does not account for the progressive development of decompensation

Table 2.2 Causes of death in compensated and decompensated cirrhosis

	Compensated ($n=377$)		Decompensated ($n=333$)	
Cause of death	No.	%	No.	%
Total number of deaths	65	17	295	86
Bleeding	12	3	52	16
Liver failure	9	2	99	30
HCC	4	1	91	27
Sepsis	3	0.1	13	4
Malignant tumors	8	2	8	2.4
Heart ischemic disease	4	1	–	–
Stroke	7	2	5	1.5
Other	11	3	8	2.4
Undefined	7	2	16	5

Data from D'Amico G, Pasta L, Madonia S, Tarantino G, Mancuso A, Malizia G, et al. The incidence of esophageal varices in cirrhosis. Gastroenterology 2001;120:A2

and for the increased risk of death after decompensation. As a consequence, the increased risk of death after decompensation is unduly associated with a presentation of compensated cirrhosis.

In recent years, the use of competing risks analysis has shown that mortality of compensated patients while they are still compensated is very low, because most of them die only after developing decompensation. The competing risks approach allowed to measure the intensity of transition from compensated to decompensated cirrhosis before death, therefore introducing the concept of clinical stages and transition across them [3]. Compensated and decompensated cirrhosis have been therefore considered as two distinct entities characterized by different clinical course, different survival, different prognostic indicators, and different causes of death [2, 3] (Table 2.2). This concept posed the study of the clinical course of cirrhosis in a very different perspective compared to the traditional approach of previous studies. A four-stage system was initially proposed [3] which was subsequently modified into a five-stage one [16]: two stages in compensated and three in decompensated cirrhosis. The following summary of the outcome of cirrhosis is drawn from unpublished data from a multicenter retrospective study of clinical stages of cirrhosis [16]:

- *Stage 1* is characterized by the absence of esophageal varices in compensated patients. While patients remain in this stage, the 1-year mortality rate is 1.5 % (Fig. 2.1). Patients exit this stage at a cumulative rate of 11.9 % per year: 6.2 % because of the development of varices and 4.2 % because of decompensation, mostly marked by development of ascites.
- *Stage 2* is characterized by the presence of esophageal varices with compensated cirrhosis. While patients remain in this stage, the 1-year mortality rate is 2 %. Patients leave this stage also by developing decompensation (12.2 % per year) (Fig. 2.1), mostly characterized by bleeding or ascites.
- *Stage 3* is characterized by upper digestive bleeding without other decompensating events. While patients remain in this stage, the 1-year mortality rate is

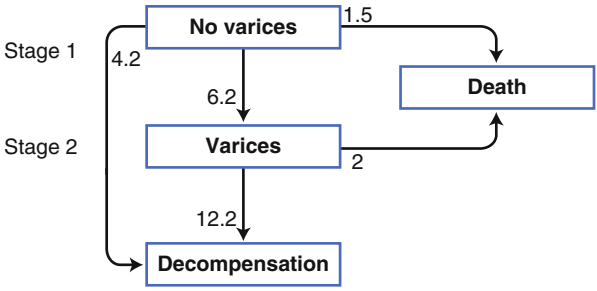

Fig. 2.1 One-year outcome of patients with compensated cirrhosis according to the absence (stage 1) or presence (stage 2) of esophageal varices

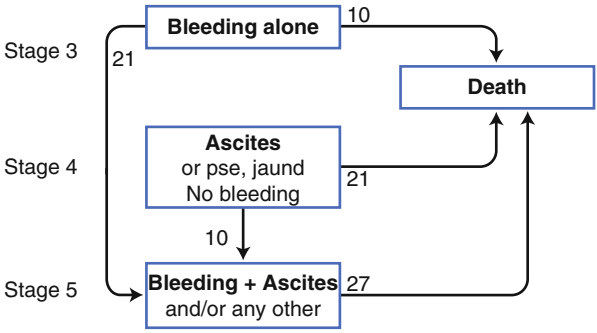

Fig. 2.2 One-year outcome of patients with decompensated cirrhosis according to development of bleeding alone (stage 3), ascites, or other decompensating events (stage 4) and to the presence of two or more decompensating events (stage 5)

10 % per year, significantly higher than in the two former stages (Fig. 2.2). Twenty-one percent of patients also exit this stage by developing other decompensating events (mostly ascites).

- *Stage 4* is characterized by ascites, jaundice, or encephalopathy. In this stage the 1-year mortality rate is 21 %, while 10 % of patients develop further decompensating events thus transitioning in stage 5.
- *Stage 5* is characterized by more than one decompensating event thus indicating a more advanced liver dysfunction. One-year mortality in this stage is 27 %. To note, a total of 87 % of these patients die within 5 years, mostly after developing further decompensating events.

HCC develops at a fairly constant rate of 3 % per year and is associated with a worse outcome at whatever stage it develops.

Although several studies [4, 17, 18, 61] have confirmed the rationale for a staging system in cirrhosis, a full independent and prospective validation of the proposed system is still awaited. Potential advantages of this staging system are the easy applicability and reproducibility. It may also contribute to identify more accurate predictors of the outcome within each single stage. It is in fact conceivable that prognostic scores such as the MELD [21] or the Child-Pugh [29] or other predictors may have a different impact in different stages. In fact, an exploratory unpublished prognostic analysis in a prospective cohort study [11] showed that the most important prognostic indicators yielded markedly different hazard ratios according to whether they were adjusted or not for the clinical stage.

Acute-on-Chronic Liver Failure

Decompensation of cirrhosis may present acutely with ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and bacterial infections that lead to hospitalization. On admission, some of these patients have only decompensated cirrhosis, whereas others may exhibit decompensated cirrhosis associated with newly developed liver and/or extrahepatic organ failure. Patients with cirrhosis and acute organ failure are at high risk for short-term death and this condition has been termed ACLF in the recent years [62]. It is associated with very high mortality and its prevention should be considered a major aim in cirrhosis management strategies.

A universally accepted definition of ACLF is still lacking. In Western countries, it has been suggested that ACLF be defined as an acute deterioration of liver function in patients with cirrhosis that is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality. Based on the association of liver dysfunction with liver or other organ failure, ACLF has been classified in four grades from 0 (merely decompensated cirrhosis) to grade 3, depending on the number and severity of associated organ failure [62]. Twenty-eight day mortality has been reported 5 % for grade 0, 22 % grade 1, 32 % grade 2, and 76 % grade 3.

Prognostic Indicators

In a systematic review of 118 prognostic studies of cirrhosis [3] a total of 174 different variables were evaluated. The variable that was found to be the most common independent predictor of death was the Child(-Pugh) score, having been introduced in a multivariable analysis in 67 studies and having been among the first five significant predictors in 42 (63 %) of them. This was followed by all components of the Child-Pugh score (albumin, bilirubin, ascites, encephalopathy, prothrombin time). Age was the only variable that is not part of the Child-Pugh score, which was found to be predictive of survival in more than ten studies. Among variables found to be independently predictive of survival in at least one study, HVPG, MELD, and the presence of HCC were remarkable because they were found to be predictive of death in over two-thirds of studies in which they were evaluated. Almost half of the variables evaluated were not significant in any study and, remarkably, ALT had been non-predictive of death in 31 studies in which it was evaluated. When restricting the analysis to 31 studies that met criteria for "good" quality [3], the same most common prognostic variables were confirmed: Child-Pugh score or its components and age.

When the analysis was performed separately for studies that included only compensated or only decompensated cirrhotic patients, the most common prognostic variables in each group were different, with variables related to portal hypertension (platelet count, varices, spleen size), liver function (bilirubin, albumin, prothrombin), gender, and age, appearing in the compensated group, and variables related to Child-Pugh score, bleeding, renal insufficiency, or HCC appearing in the decompensated group.

Concluding Remarks

Compensated cirrhosis is characterized by a very low mortality, while transition to decompensation is the major outcome for this early disease stage. Once decompensation occurs, the mortality rate is very high, with a median survival time of approximately 2–4 years. Esophageal varices, ascites, bleeding, jaundice, and encephalopathy allow identification of five disease stages with significantly different outcome: two stages in compensated and three in decompensated cirrhosis. In most patients the occurrence of sepsis or renal failure, with or without ACLF, will accelerate the final course towards death. A schematic representation of the clinical course of cirrhosis is reported in Fig. 2.3.

Overall, the most robust predictors of survival are the Child-Pugh [29] score or its components, age, portal hypertension, renal function, and MELD [21]. Predictors of survival are different in compensated and decompensated patients with portal hypertension assuming a greater importance in compensated patients, while in patients with decompensated cirrhosis it is the Child-Pugh score as well as renal dysfunction parameters that carry a greater weight. For present day clinical practice, Child-Pugh [29] and MELD [22] scores are appropriate survival predictors. In future studies, prognostic indicators should be assessed separately in patients with compensated and decompensated cirrhosis. In fact, in patients with compensated cirrhosis the transition to a decompensated stage may be a major endpoint for which prognostic indicators should be assessed.

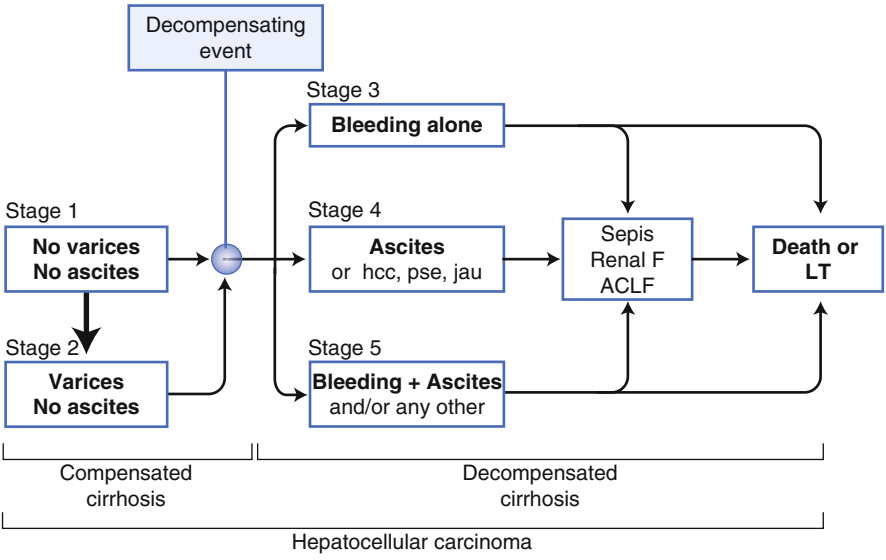

Fig. 2.3 Schematic representation of the clinical course of cirrhosis

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Chapter 3
Diagnosis of Esophageal Varices

Massimo Primignani

Introduction

Esophageal varices are submucosal veins which develop as a result of portal hypertension, either due to liver cirrhosis, the most common cause of portal hypertension in western countries, or due to other portal hypertensive conditions, more prevalent in developing countries, overall included in the large category labeled "non-cirrhotic portal hypertension." Esophageal varices, as well as gastric varices, various venous collaterals of the abdominal wall, rectal varices, and retroperitoneal collateral veins, can be regarded as an attempt to decompress the hypertensive portal venous system into the systemic circulation, bypassing the liver. Among all the portocollateral vessels, esophagogastric varices are the most relevant, given that bleeding from esophagogastric varices is the most critical complication of portal hypertension.

Because of increased portal vein pressure, blood from the short gastric and coronary veins, which normally flows in a caudal direction into the portal vein and the liver, reverses its flow and runs upwards into the submucosal esophageal veins (which enlarge and become varices) and then enters the azygos vein to reach the systemic circulation.

Although portal hypertension is by far the most common underlying condition for esophageal variceal development, other rare causes exist in which portal hypertension is not involved. Rarely, obstruction of the superior vena cava or the azygos vein, mainly due to bronchogenic carcinoma or other mediastinal disease, causes the development of a collateral circulation from the upper arms, head, and thorax through the inferior thyroid vein and mediastinal veins into the esophageal veins, which enlarge,

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and then into the portal vein via the left gastric vein, with a "downhill" flow which is the reverse of the common "uphill" flow due to portal hypertension.

Esophageal varices occur in about 60 % of decompensated and in 30 % of compensated cirrhotic patients, eventually develop in almost all, and have a tendency to increase in size with time. The presence of varices also indicates disease progression and worse prognosis in compensated patients [1]. Moreover, the diagnosis of varices is also relevant because there are effective treatments, either pharmacological or endoscopic, for the prevention of bleeding. Indeed, bleeding from esophageal varices is the most frightful complication of portal hypertension, still carrying the highest mortality rates of any of the major causes of bleeding, despite the therapeutic advances achieved in the last decades. As many as 5 % of patients with acute variceal bleeding die before hospital admission and a further 11–20 % die within 6 weeks, because of uncontrolled bleeding, early rebleeding, or the consequences of the bleeding episode. Finally, patients who survive have a high risk of rebleeding, unless they are treated to prevent it. Hence, the development of esophageal varices can be considered as a key point in the natural history of portal hypertension and the assessment of their presence and grading is a mainstay in the management of patients with chronic liver disease and is required in all patients in whom liver cirrhosis or portal hypertension from any cause is diagnosed. For these reasons, current guidelines recommend that all cirrhotic patients should be screened by esophagogastroduodenoscopy (EGD) for the presence of esophageal varices when the diagnosis of cirrhosis is established, in order to assess the bleeding risk and to implement therapeutic measures, if needed.

EGD is, at present, the gold standard for diagnosis of esophageal varices. Its accuracy is greater than that of radiology (including multidetector CT-angiography) mainly because it allows the detection of indicators of bleeding risk, such as the red color signs, that cannot be detected by other imaging techniques. Besides its diagnostic accuracy, endoscopy allows assessment of gastric varices and other portal hypertension-related lesions of the upper gastrointestinal tract, such as portal hypertensive gastropathy or gastric vascular ectasia.

Endoscopic Examination

It is generally agreed that all patients with a diagnosis of cirrhosis should be screened for varices with an EGD. If no varices are seen, a further EGD should be performed in 2–3 years. If small varices are seen, repeat EGD should be performed in 1–2 years or earlier if patients show evidence of decompensation [2].

The endoscopic diagnosis of esophageal varices is usually easily made. However, some rules must be applied to avoid diagnostic errors, which are possible, particularly in case of small esophageal varices, which must be differentiated from esophageal folds. The assessment of esophageal varices should be carried out during withdrawal of the endoscope, maintaining the esophagus well inflated with air and the stomach empty. Such a manoeuvre flattens out the esophageal folds that could

otherwise be misdiagnosed as small varices. Other criteria that can differentiate small varices and esophageal folds are the color and the shape, since varices may be bluish in color and tortuous, whereas the mucosal folds are always linearly shaped and white or of normal esophageal color. However, such criteria may be confusing since small esophageal varices can be linear and not bluish. Hence, it may be sometimes difficult to distinguish folds from small esophageal varices.

At EGD, esophageal varices appear as single or, more often, multiple blue or white raised structures, linear, tortuous, or nodularly shaped, running longitudinally in the submucosa of the esophageal wall. Although large varices are often blue and small varices are often white, this finding is inconstant and has not proved to be of prognostic value for the assessment of the bleeding risk. Concerning their location, in most cases esophageal varices are not present in the cervical esophagus, but can be observed in the middle and distal esophagus, starting from 25 to 30 cm from the incisors, at the level of the azygos vein. Rarely, when portal hypertension is particularly severe and esophageal varices particularly huge, they can extend into the cervical esophagus, which indicates a very high portocollateral flow. In the distal esophageal tract the variceal size typically increases. After the cardia is entered, the varices go deeper in the cardial submucosa, and often can no longer be detectable [3]. Such a deep submucosal location, as compared to the superficial position in the lower esophagus, accounts for the higher risk of bleeding in the lower esophagus just above the gastroesophageal junction rather than below it, in the cardia. As a general rule, the larger the size of esophageal varices, the greater the risk of variceal hemorrhage [4–6].

Other important features of esophageal varices that can be easily recognized at endoscopy are the red signs overlying the varices. There are four types of red signs: the red wale marks, which appear as red streaks on the variceal surface and represent dilated venules overlying the variceal wall; the cherry red spots, which are small circular dots less than 2 mm in diameter; the hematocystic spot, which is a usually single, large, raised red lesion similar to a blister, infrequently observed, but considered as a sign of impending bleeding risk; and diffuse redness, which is a red area over one or more varices.

Grading of Esophageal Varices

Besides variceal size, which is the most important risk factor for bleeding, further risk factors are the presence and extent of the red color signs and, from the clinical standpoint, the severity of the underlying liver disease. Since the varices in the lower esophagus are at the highest risk for bleeding, the grading of esophageal varices should refer to their endoscopic appearance in such location. A detailed description of esophageal varices should therefore include their size, the presence, type, and extent of the red color signs, and, possibly, the extent of their location in the esophagus (lower, middle, or upper).

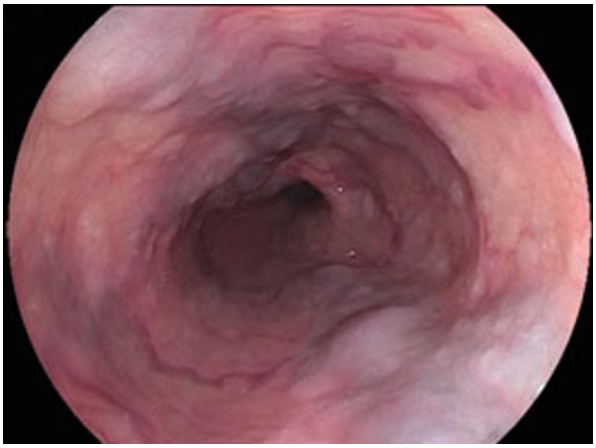

Fig. 3.1 Linearly shaped, small, bluish esophageal varices

Several grading systems have been devised which take into account the endoscopic features just described. The current most popular classification is by the Japanese Research Society for Portal Hypertension [7]; and by the North Italian Endoscopy Club for the Study and Treatment of Esophageal Varices [4]. The Japanese classification entails an accurate description of the location (upper, middle, or lower third of the esophagus), form (F1: small and straight; F2: enlarged and tortuous; F3: large and coil-shaped), fundamental color (white or blue), and red color signs. The NIEC classification, besides grading the variceal size as small, medium, or large and the presence of red color signs as absent, mild, moderate, or severe, takes into account also the severity of cirrhosis, as assessed by the Child-Pugh class, given that, for equivalent endoscopic features of esophageal varices, it demonstrates that the bleeding risk is higher in Child-Pugh C patients than in Child-Pugh B or A patients [4].

However, when assessed prospectively, both classification, although confirming their high specificity, demonstrated low sensitivity and predictive value, since patients with the highest risk for bleeding could be correctly recognized, but only a minority of patients who will eventually bleed fell into the highest-risk categories [8]. Other limitations of these detailed grading systems are their subjectivity and, as a consequence, a limited reproducibility [9–11]. Moreover, these grading systems were devised as prognostic indexes of the first variceal bleeding before the widespread use of propranolol to prevent variceal bleeding had occurred, and their effectiveness was not subsequently evaluated in patients on beta-blocking drugs. All in all, although these grading systems continue to be used, either for clinical research or for daily practice, it was agreed that a more simple and possibly reproducible classification might be more useful. The Baveno I consensus conference [12] in 1992 recommended that esophageal varices be classified as small (<5 mm) (Fig. 3.1) and large (>5 mm) (Fig. 3.2), being 5 mm the size of an open biopsy forceps.

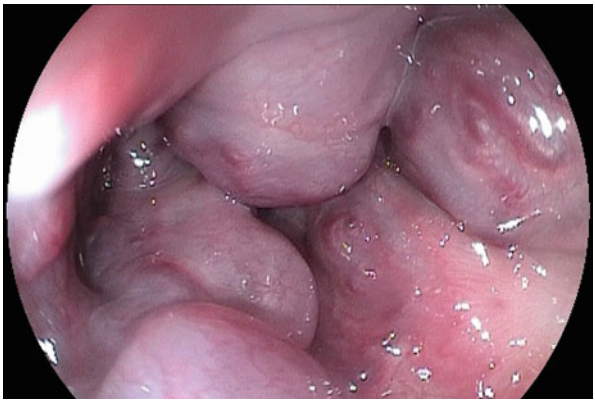

Fig. 3.2 Large esophageal varices with red color signs (red wale markings)

Concerning the other endoscopic features included in current classifications (color, form, location, appearance of the surface, number of chords), only the red color signs on varices have been perceived as important. The 5 mm cut-off was subsequently confirmed as the best one to discriminate small from large varices [10], which has practical implications since large varices warrant prophylaxis, either pharmacological, if tolerated and not contraindicated, or endoscopic, with esophageal variceal ligation. However, besides variceal size, which is recognized as the most relevant prognostic indicator of the bleeding risk, the presence and intensity of the red color signs on the variceal wall and an advanced Child-Pugh class are confirmed additional risk factors [13] and should be considered, as in the NIEC index, when assessing the risk of first bleeding. As a consequence, Child-Pugh C patients, even if with small varices (but with positive red color sign), have also been identified as worthy of prophylaxis [14].

Besides esophageal varices, EGD can identify gastric varices as well other portal hypertensive-related mucosal lesions, such as portal hypertensive gastropathy and gastric antral vascular ectasia, which may be a relevant cause of bleeding in cirrhotic patients. The description and classification of these lesions are beyond the purpose of this chapter.

Endoscopic Diagnosis of Esophageal Variceal Bleeding

When a patient with cirrhosis presents with upper gastrointestinal bleeding, varices are the cause in 70–80 % of cases [15]. Therefore, for practical purposes, upper gastrointestinal bleeding in a cirrhotic patient should be considered of variceal origin, and treated accordingly together with early administration of vasoactive drugs, appropriate volume replacement, blood transfusion to keep hemoglobin levels at 8 g/dL, and antibiotic prophylaxis, which are the standard of care of the early

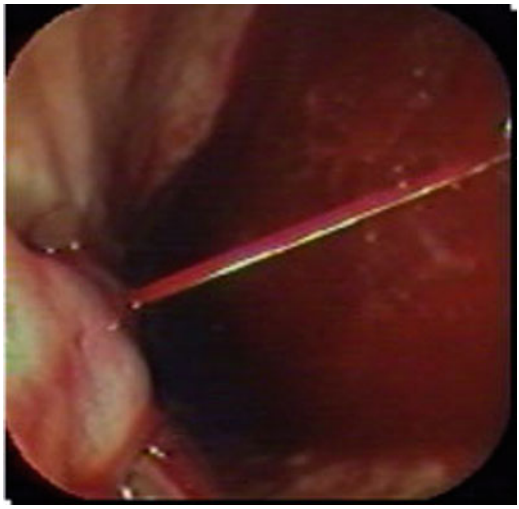

Fig. 3.3 Acute variceal bleeding: a venous (nonpulsatile) spurt from a varix

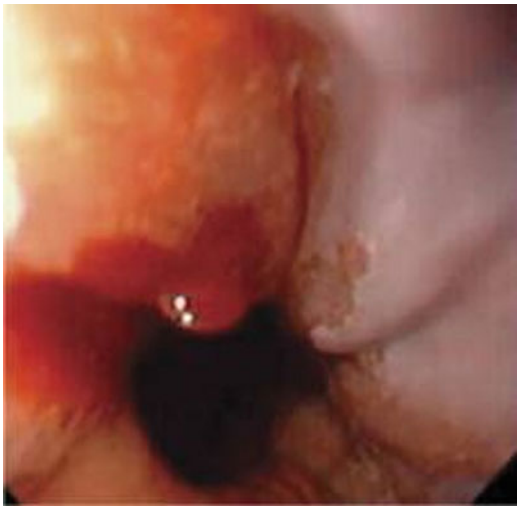

Fig. 3.4 Acute oozing variceal bleeding just above the esophagogastric junction

management of variceal bleeding. EGD, which must be performed as soon as resuscitation is adequate and preferably within 12 h from the index bleed, is the gold standard for diagnosis. It may reveal a venous (nonpulsatile) spurt from a varix (Fig. 3.3) or blood oozing from a varix (Fig. 3.4) or at the gastroesophageal junction, but these direct features of variceal bleeding can be seen in no more than 20 % of cases. Other features, visible when bleeding is ceased, are the "white nipple sign" (Fig. 3.5), a discrete, raised, white or reddish point which represents the site of

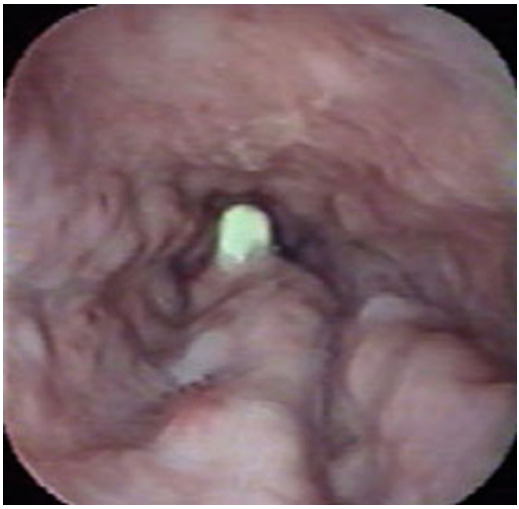

Fig. 3.5 The "white nipple sign" represents the certain sign of a recent variceal bleeding

blow-out after disruption of the clot, or a clot adherent to a varix. In most instances, however, the stomach is filled with fresh blood and clots, and diagnosis of the bleeding site is complicated by the continuous reflux of blood from the stomach into the esophagus. As a general rule, if the source of bleeding is in doubt but no other lesion can be seen other than varices, these may be assumed to be the source of bleeding.

Noninvasive Diagnosis of Esophageal Varices

As stated previously, esophageal varices are present in about 60 % of decompensated, but in only 30–40 % of compensated, cirrhotic patients [1]. Moreover, large esophageal varices, generally the only ones deserving prophylaxis according to current guidelines, are more rarely found in compensated cirrhotic patients. Indeed, the prevalence of esophageal varices in a large cohort of patients with compensated hepatitis C virus-related liver disease (bridging fibrosis or cirrhosis) was around 25 %, but they were large sized in 1.2 % of cases only [16].

Therefore, particularly in compensated cirrhotic patients, the recommendation to perform an EGD when cirrhosis is diagnosed, certainly, is not cost-effective. Such a policy causes a load of negative, hence avoidable, costly, and invasive procedures, often not well accepted by the patient and taxing for the endoscopy unit. Indeed, it has been shown that up to 50 % of patients with cirrhosis may not have developed esophageal varices 10 years after the diagnosis. Therefore, the possibility of a noninvasive screening to identify patients with esophageal varices, or with large esophageal varices, has been perceived as an important issue and has led to the proposal of many noninvasive or minimally invasive tests or procedures to be

used as surrogate markers of clinically significant portal hypertension, with the purpose of selecting for endoscopy only those patients at high risk of carrying esophageal varices, thus saving a lot of superfluous endoscopies. Such tests include hemometric parameters, such as the platelet count, splenomegaly, or a combination of these two parameters (i.e., the ratio of platelet count to spleen size measured on ultrasound); other ultrasound findings include a portal vein diameter of 13 mm or above, and a reduced blood flow velocity, measured by Doppler ultrasound. More recently, new tools that can evaluate fibrosis noninvasively, such as Fibrotest (a panel of biochemical markers) and transient elastography (Fibroscan), which allows the assessment of liver stiffness and spleen stiffness, have been evaluated for the noninvasive diagnosis of esophageal varices. Finally, other diagnostic imaging techniques, such as multidetector CT-angiography or spleen MRI, can also inform on the presence and grading of esophageal varices and have been compared with EGD in several studies. In the next paragraphs, because of the limited space for this chapter, only some of these tests or techniques will be briefly commented on. However, it must be anticipated that, for the present time, none of them has been proven accurate enough or has gained enough popularity to be used as a substitute of EGD in the assessment of esophageal varices, except in selected situations.

Platelet Count and Platelet Count/Spleen Diameter Ratio Index

Several studies have shown that a low platelet count is a predictor of esophageal varices [6, 16–24] or of large esophageal varices [16–18, 20, 21, 23–25]. Unfortunately, the discriminating threshold for the presence of varices in these studies ranged between 68,000 and 160,000/mm^3, thus indicating the poor reproducibility of these findings. Among these studies, one of the most relevant [16], which included more than 1,000 patients with HCV-related advanced fibrosis or cirrhosis resistant to antiviral treatment, found that a platelet count above 150,000/mm^3 could exclude the risk of having large esophageal varices with a sensitivity of 90 % and a negative predictive value of 99 %. However, it was observed that a platelet count above 150,000/mm^3 is quite infrequent in cirrhotic patients and this hampers the relevance of this finding.

Giannini et al. [26], by combining the platelet count and the spleen longitudinal diameter, measured on ultrasound, proposed the platelet count/spleen diameter ratio as a noninvasive index of esophageal varices. In the original study, a cut-off of 909 had positive and negative predictive values for the presence of esophageal varices of 96 and 100 %, respectively, Indeed, a negative predictive value of 100 % would be perfect for screening purposes. Unfortunately, the multicenter prospective validation study [27] planned to validate the platelet/spleen diameter ratio in predicting the presence of esophageal varices demonstrated that the performance of the test was significantly lower than in the original study, because the cut-off of 909 had an

accuracy of 86 %, 91.5 % sensitivity, 67 % specificity, 76.6 % positive predictive value, and 87 % negative predictive value. Therefore, the platelet count/spleen diameter ratio index has not been adopted in clinical practice.

Transient Elastography (Fibroscan) and Fibrotest

Transient elastography uses pulse-echo ultrasound to measure liver stiffness, a surrogate marker of liver fibrosis. Given that advanced fibrosis leads to portal hypertension, several studies [28–33] evaluated whether liver stiffness could be able to predict the presence of esophageal varices. Generally, these studies show that liver stiffness can be correlated with the presence or even the grade of esophageal varices, with variable accuracy and with different cut-off values.

A study comparing the ability of platelet count, spleen diameter, liver stiffness, and combinations of these factors [i.e., ratio of platelet count to spleen size, and liver stiffness × spleen size/platelet count (LSPS)] [33] showed that the combination of data on liver stiffness, spleen diameter, and platelet count had the best accuracy in identifying patients with compensated cirrhosis most likely to have esophageal varices, correctly classifying 85 % of patients with esophageal varices in the training set, although 75 % only in the validation set.

Since portal hypertension leads to spleen congestion and fibrosis, transient elastography was also used to measure spleen stiffness [34, 35]. Indeed, spleen stiffness was significantly higher in patients with varices than in those without varices, although no differences could be found between patients with varices of different sizes. In one of these studies [34], spleen stiffness significantly outperformed LSPS and platelet/spleen ratio, but not liver stiffness, in the prediction of varices. Attempting to summarize the results from these studies, it appears that, although transient elastography is a good noninvasive tool for the detection of esophageal varices, its accuracy and reproducibility are currently deemed insufficient to be used in clinical practice and to replace endoscopy in the assessment of esophageal varices. Therefore its use should be limited to those patients unwilling to undergo invasive procedures. Limitations of transient elastography include obesity, patients with a narrow intercostal space, and the presence of ascites. Up to 20 % of measurements can be unreliable because of these limitations. Moreover, tissue abnormalities other than fibrosis, such as oedema and inflammation, cholestasis, or congestion have been shown to interfere with liver stiffness measurements.

Fibrotest is a panel of biochemical markers (γ-glutamyltranspeptidase, haptoglobin, bilirubin, apolipoprotein A, alpha-2-macroglobulin) developed as a surrogate indicator of fibrosis. One study [36] addressed its performance in identifying patients with large esophageal varices, and compared it with that of platelet count and Child-Pugh score. For a cut-off value of 0.8, Fibrotest had 92 % sensitivity and 21 % specificity. Although Fibrotest performed better than platelet count and Child-Pugh score for the detection of large esophageal varices, its accuracy was finally judged as inadequate.

Minimally Invasive Diagnostic Tools

Ultrathin endoscopy and capsule endoscopy are minimally invasive diagnostic tools. Ultrathin endoscopy utilizes a 3.1-mm battery-powered esophagoscope, better tolerated than a regular endoscope. Hence it does not require sedation and is indicated for patients in whom sedation is contraindicated or for those who are unwilling to undergo regular endoscopy. A small pilot study [37] comparing ultrathin endoscopy and standard endoscopy showed that ultrathin endoscopy had a sensitivity and negative predictive value of 100 % with a specificity and positive predictive value of 93 % for the detection of esophageal varices. Larger studies are needed to confirm these results.

Capsule Endoscopy

In recent years, an esophageal endoscopic capsule (PillCam ESO), that allows a minimally invasive evaluation of the esophagus, became available. The capsule, which measures 26 by 11 mm, transmits 14 images per second to a recorder that the patient carries on a belt. After the procedure, the recorder is connected to a workstation and the images can be observed.

Capsule endoscopy has been used for the screening and surveillance of esophageal varices in patients with cirrhosis in three pilot studies [38–40]. The concordance of the capsule findings with those of conventional EGD for the presence of varices was 97 %, 84 %, and 100 %, respectively. In addition, the grading of varices was also assessed in one of these studies [41], showing a good concordance between the two techniques. In the first prospective multicenter study comparing capsule endoscopy to EGD [41] in 228 subjects, the sensitivity, specificity, positive predictive value, and negative predictive value to detect varices were 84 %, 88 %, 92 %, and 77 %, respectively. Concerning grading, a 91 % agreement was found between the two techniques to distinguish small from large varices. As expected, patient satisfaction was higher for capsule endoscopy. Unfortunately, such satisfying results could not be fully reproduced either in a similar, although smaller, study [42] which found a sensitivity of 63 % and specificity of 82 % for the diagnosis of large varices, but an inter-observer agreement of only 0.56, or in a subsequent, prospective multicenter study [43] in which the sensitivity and specificity for the detection of varices by capsule endoscopy were only 77 % and 86 %, respectively. Finally, a meta-analysis [44] of these studies provided a pooled sensitivity and specificity of 85.8 % and 80.5 %, respectively, for detection of esophageal varices. In summary, although attractive because of its minimal invasiveness and high tolerability, capsule endoscopy appears to be less effective than standard endoscopy for detection of esophageal varices and should be reserved to patients not able or unwilling to undergo a standard EGD.

Concerning tolerability, satisfaction, and acceptance, the three available endoscopic techniques—sedated conventional endoscopy, unsedated ultrathin endoscopy, and esophageal capsule endoscopy—were compared in a small pilot study [45], in which the patients were consecutively submitted to the three procedures. Capsule endoscopy caused less pain and discomfort as compared to the other two techniques and more patients would repeat esophageal capsule endoscopy in the future.

Computed Tomography and Magnetic Resonance Imaging

Besides the evaluation of the liver size and profiles, computed tomography (CT) allows the assessment of other features of portal hypertension such as ascites, splenomegaly, and portocollateral circulation. Several studies [46–48] have compared CT with EGD for the assessment of esophageal varices. With different techniques (single versus multidetector) these studies showed 63–93 % sensitivity for the detection of esophageal varices of any size and of 56–92 % for the detection of large varices. The specificity ranged from 76 % to 97 % and from 84 % to 92 %, respectively. Concerning the grading of varices, either helical CT [46] or CT esophagography [47] showed a good correlation with endoscopy. However, CT esophagography, besides using radiation, requires a plastic tube to be passed through the mouth to inflate the esophagus so that its minimal invasiveness might be questioned. Because of the additional information concerning extraluminal pathology, the preference of patients for CT over (unsedated) endoscopy, and a favorable cost-effective analysis, the investigators of one of these studies [48] concluded that CT might be preferred to endoscopy as the first screening tool for variceal detection.

Magnetic Resonance Imaging (MRI) provides an excellent view of the vascularization of the liver and the portocollateral circulation [49]. The performance of gadolinium-enhanced MRI to identify varices was evaluated [50], showing an 81 % sensitivity and a good correlation with the grading of esophageal varices assessed on endoscopy.

MRI was also used to assess spleen stiffness [51], and such measurement was correlated with the occurrence of esophageal varices in a pilot study which showed a specificity higher than liver stiffness, also evaluated with MRI. This new technique, however, is not widely available and, for the present time, its use as a screening tool cannot be considered.

Conclusions

There is no doubt that diagnosing and grading esophageal varices are of vital importance in patients with cirrhosis. In compensated patients, the presence of varices is an index of disease progression and if varices are large they require treatment to

prevent bleeding. Therefore, current guidelines recommend that all patients in whom cirrhosis is diagnosed undergo endoscopic screening for varices and repeat endoscopy at 2–3 years intervals if varices are not found and the disease is compensated, or after 1 year for those with decompensated disease, in order to implement effective therapeutic measures to prevent bleeding, if required.

However, and particularly in compensated patients, esophageal varices occur in only about 30 % of cases, and up to 50 % of patients may still not have varices 10 years after the diagnosis of cirrhosis. Hence, a huge number of avoidable, unpleasant, and costly endoscopies are performed, which could be avoided if accurate noninvasive tools to diagnose esophageal varices, and particularly large esophageal varices, were available. Unfortunately, of the noninvasive or minimally invasive tests or procedures proposed as alternative to endoscopy, none has become of current use in clinical practice, because of insufficient accuracy or lack of adequate validation.

However, their performance is different. Among the tests based on clinical, biochemical, and ultrasound parameters, the platelet count/spleen diameter ratio is probably the best, although its accuracy in the validation study [27] was lower than in the original study [26] and further evaluation in different patient populations should be performed. None of the other tests in this category appears to fulfill the requisite of a sufficient accuracy to replace EGD or select patients in whom EGD could be avoided. Transient elastography needs standardization and, at present, suffers of several limitations that hamper its applicability. Moreover, liver stiffness shows a good correlation with the level of portal hypertension, while its performance in diagnosing esophageal varices is lower.

The performance of multidetector CT scanning appears to be good, although the technique, particularly if a plastic tube must be used to inflate the esophagus as in CT esophagography [47], is not minimally invasive and should be compared with "sedated" rather than "unsedated" endoscopy. In general, CT scanning appears a good screening tool for the detection of esophageal varices, but further studies are needed to corroborate the results of the first studies.

Besides variceal size, other endoscopic features of esophageal varices, namely the presence and intensity of the red color signs, do have an impact on the bleeding risk, but cannot be assessed by the diagnostic tools described previously, apart from ultrathin endoscopy, which is very rarely available, and capsule endoscopy, whose performance is, at present, lower than that of standard endoscopy [41]. However, technical improvements are in progress and will probably lead to a better performance of capsule endoscopy. For the present time, capsule endoscopy could be proposed to patients unwilling or unable to undergo EGD.

In conclusion, several tools have been proposed for the noninvasive diagnosis of esophageal varices, and some of these are promising for the future. However, for the time being, the Baveno IV consensus statements [14] that "there are no satisfactory nonendoscopic indicators for the presence of varices" and that "all cirrhotic patients should be screened for varices at diagnosis by EGD" still stand.

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Part II
Preventing the First Variceal Hemorrhage

Chapter 4
Assessing the Risk of Bleeding

Roberto de Franchis

Abbreviations

HVPG	Hepatic vein pressure gradient
NIEC	North Italian Endoscopic Club
TIPS	Transjugular intrahepatic portosystemic shunt

Introduction

Longitudinal studies [1] have shown that, although all patients with cirrhosis will eventually develop varices, only a proportion of them will bleed. In the untreated or placebo-treated control groups of randomized controlled trials for the prevention of the first variceal hemorrhage with beta-blockers, sclerotherapy or rubber band ligation, carried out in the 1980s and 1990s [2, 3], the 2-year incidence of variceal bleeding ranged between 18 and 60 %, with a mortality rate ranging between 18 and 58 %. When a patient bleeds from varices, current guidelines [4] recommend using a combination of endoscopic therapy (preferably rubber band ligation) and vasoactive drugs (terlipressin, somatostatin, or octreotide). This approach has improved the outcome of bleeding patients [5]. However, failure to control bleeding still occurs in 10–42 % [6] of patients, with a 5-day mortality ranging between 3 and 14 %, and, in recent series, the 30-day or 6-weeks mortality still ranged between 11.1 [7] and 19.8 % [8]. Patients surviving an episode of variceal hemorrhage have a very high risk of rebleeding; in the randomized controlled trials of secondary prophylaxis with sclerotherapy, rubber band ligation [3], or beta-blockers [2], in

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which the control group patients were left untreated or given a placebo, the 1- or 2-year incidence of rebleeding ranged between 32 and 84 %, and the corresponding mortality ranged between 11 and 44 %.

These data highlight the great variability of the risks of first bleeding, of failure in bleeding control, and of rebleeding. Since variceal bleeding and rebleeding still carry a high short- and long-term mortality, identifying in advance the patients at risk of adverse outcomes might help choosing the most effective form of treatment in each situation. The present chapter will analyze the current knowledge on the prediction of the first variceal hemorrhage, of the failure of first-line treatments for acute bleeding, and of rebleeding.

Prediction of the First Variceal Hemorrhage

It is known that variceal bleeding does not occur below a portal pressure threshold value (as measured by the hepatic vein pressure gradient—HVPG) of 12 mmHg [9]. However, measurement of the HVPG in routine clinical practice is impractical. On the other hand, the risk of bleeding is related to the size of varices [10]. It is therefore logical to use variceal size at endoscopy as a criterion to identify patients at risk of bleeding.

Early Attempts

Since the early days of flexible endoscopy, attempts have been made at classifying varices into risk classes for bleeding. In 1966, Dagradi et al. [11] published an endoscopic classification in which varices were divided into four classes of increasing risk for bleeding, based mainly on their size.

In 1980, the Japanese Research Society for Portal Hypertension [12] published a much more detailed classification, in which several endoscopic features of varices such as size, color, location, longitudinal extent, presence of red wale markings, cherry-red spots, hematocystic spots, diffuse redness, and esophagitis were taken into consideration. In 1987, the Italian Liver Cirrhosis Project [13] evaluated the reliability of endoscopy in the assessment of the variceal features of the Japanese classification; in that study the interobserver agreement between endoscopists in classifying the various features of varices was evaluated by kappa statistics using a semiquantitative rating system. The authors concluded that the agreement was fair to good for location, size (Fig. 4.1), and lumen occupancy of varices, presence of blue color, presence and extension of red color signs and hematocystic spot. Using the Japanese classification, in 1981 Beppu et al. [14] published the results of a retrospective study of 172 cirrhotic patients with varices, 90 of whom had had a previous variceal bleed. In that study, they analyzed by discriminant analysis the relationship of various endoscopic features of varices with previous bleeding and

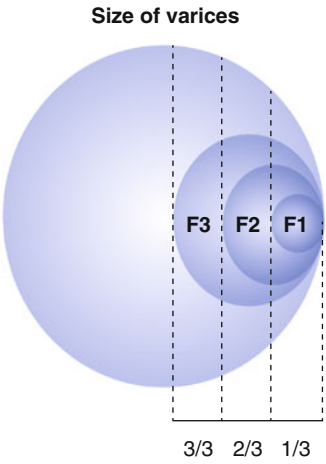

Fig. 4.1 Size of varices as classified by the Italian Liver Cirrhosis Project. (Created using data from Italian Liver Cirrhosis Project. Reliability of endoscopy in the assessment of variceal features. J Hepatol 1987;4:93–98)

found that previous bleeding was strongly related to the size, the blue color of varices, the presence of cherry red spots, hematocystic spots, red wale markings on the variceal surface and esophagitis. Using the results of the discriminant analysis, Beppu et al. developed a variceal scoring system to quantitatively express the predictability of bleeding. The variceal score allowed them to stratify patients into six risk classes, in which the occurrence of previous episodes of bleeding ranged from 0 to 100 %.

The NIEC Index

Beppu's paper inspired the investigators of the North Italian Endoscopic Club (NIEC—a group of endoscopists and hepatologists from several centers in Northern Italy) to conduct a prospective multicenter study [15] in 321 patients with cirrhosis and varices but with no previous bleeding, to see whether a comprehensive analysis of their clinical features and of the endoscopic appearances of their varices could help to identify those at highest risk for bleeding. Varices were classified endoscopically as suggested by the Japanese Research Society for Portal Hypertension [12]. Patients were followed for 1–38 months (median, 23), during which 85 patients (26.5 %) bled. By applying Beppu's variceal score to the population of this study, it was found that this score grossly overestimated the bleeding risk. In fact, while the 1- and 2-year rates of bleeding increased steadily from class 1 to class 6 of the score, the observed 1-year rate of bleeding in the various classes ranged between 3.4 and 42.9 %, as compared to an expected range of 0–100 %. Multiple regression analysis (Cox's model, Table 4.1) of the NIEC study population revealed that the risk of bleeding was significantly related to the patient's Child-Pugh class, the size of the

Table 4.1 Independent prognostic risk factors for the first variceal hemorrhage identified by multiple regression analysis (Cox's model)

Variable	Grade	No. of patients	% Who Bled	*P* value
Child's class	A	135	17.0	<0.0001
	B	132	31.1	
	C	54	38.9	
Size of varices	Small	160	18.1	<0.0001
	Medium	112	28.6	
	Large	49	48.9	
Red Wale Markings	–	204	19.1	=0.0179
	+	79	32.9	
	++	28	39.3	
	+++	10	80.0	

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varices, and the presence of red wale markings (longitudinal dilated venules resembling whip marks) on the varices. A prognostic index based on these variables (the NIEC index) was developed according to the formula:

$$NIEC\ Index = \left[\begin{matrix} \left(0.6450 \times Child\ class\right) + \left(0.4365 \times Variceal\ size\right) \\ + \left(0.3193 \times Red\ wale\ markings\right) \end{matrix} \right] \times 10$$

Using the NIEC Index, which ranges from <20 to >40 points, patients can be stratified into six risk classes of increasing risk. The index underwent prospective validation on an independent sample of 75 patients with varices and no history of bleeding, which showed an excellent agreement between expected and observed bleeding rates in the various classes of the index. A pocket chart for calculation of the risk of bleeding in individual patients was developed by plotting the estimated 1 year probabilities of bleeding as a function of all the possible combinations of the three variables (Table 4.2). The table shows that the probability of bleeding increases from 6 % for Child's A patients with small varices and no red signs, to 76.6 % for Child's C patients with large varices and severe red wale markings. The table underscores the prognostic importance of the red color signs; in fact, across Child's classes and variceal sizes, the presence of red wale markings on the variceal surface nearly doubles the 1-year risk of variceal hemorrhage. The NIEC Index is practical, since it can be calculated by using simple clinical and endoscopic parameters with which clinicians and endoscopists are familiar. In addition, the expected 1-year risk of variceal bleeding can be easily calculated using the pocket chart reported in Table 4.2. However, the index is not perfect, since, although the risk of bleeding increases steadily from class 1 to class 6 (Table 4.3), about one fifth of the patients

Table 4.2 One-year estimated percentage probabilities of bleeding as a function of all the possible combinations of the three variables of the NEC index

Child's class	A			B			C		
Size of varices	Small	Medium	Large	Small	Medium	Large	Small	Medium	Large
RCS									
Absent	6	10	15	10	16	26	20	30	4,236
Mild	8	12	19	15	25	33	28	38	54
Moderate	12	16	24	20	30	42	36	48	64
Severe	16	23	34	28	40	52	44	60	76

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Table 4.3 Distribution of variceal bleeds among risk classes of the NIEC index

Risk class—risk level	NIEC index value	No. who bled/total	% of total bleeds
1. Low	<20.0	6/73 (9.5)	22.2
2. Low	20.0–25.0	12/76 (15.7)	
3. Medium	25.1–30.0	14/63 (22.2)	39.6
4. Medium	30.1–35.0	18/56 (32.1)	
5. High	35.1–40.0	24/48 (50.0)	38.2
6. High	>40.0	7/11 (63.6)	

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who actually bled belonged to the two lowest-risk classes, and only about 40 % of the bleeds occurred in patients belonging to the two highest-risk classes.

Other Attempts

After the publication of the NIEC study, several other investigators addressed the issue of predicting variceal hemorrhage. Kleber et al. [16] observed that the risk of bleeding was correlated with the presence of gastric fundal varices, the size of esophageal varices, and the presence of red signs, as well as alcoholic etiology of cirrhosis. Siringo et al. [17] showed that variceal size, cherry-red spots, serum bilirubin, and congestion index of the portal vein [the ratio of portal vein (cross-sectional area) and portal blood flow velocity] were the only independent predictors of variceal bleeding. Zoli et al. [18] developed a prognostic index based on the size of esophageal varices, gastric varices, and congestive gastropathy, and claimed that it had better prognostic accuracy than the NIEC Index. Nevens et al. [19], in a prospective study of 87 patients confirmed the validity of the NIEC Index, and showed that, by adding to the NIEC score the measurement of variceal pressure by an endoscopic

pressure-sensitive gauge, a significant improvement in prognostic accuracy of the index could be obtained. Other studies identified a variety of variables related to the risk of bleeding. However, none of the other prognostic scores proposed supplanted the use of the NIEC index in clinical practice, and current guidelines state that "the NIEC score is presently the most reliable predictor of variceal rupture" [20].

In conclusion, the risk of first variceal bleeding can be predicted with a reasonable degree of accuracy by using the NIEC Index, which can be used to select patients for whom prophylactic treatment to prevent bleeding is indicated.

Prediction of the Failure to Control Bleeding and To Prevent Early Rebleeding

As stated in the introduction, current treatments can control bleeding in over 90 % of cases [6, 8]; however, the patients in whom bleeding is not controlled have a very high mortality. In 2003, a multicenter Italian survey was published, which included 465 cirrhotic patients with upper GI hemorrhage treated with endoscopic or pharmacological therapy or a combination of the two. The study included a training set of 291 patients, and a test set of 174 patients. Overall, failure to control the initial bleeding despite immediate combination of endoscopic and pharmacologic therapy and balloon tamponade as appropriate occurred in 25/465 patients (5.4 %), and 20 of them (80 %) died. Eighteen patients in whom initial bleeding control had been achieved rebleed within 5 days, and 3 of them (16.6 %) died. One might hypothesize that if these could have been identified in advance, and treated more aggressively (e.g., with early transjugular intrahepatic portosystemic shunt—TIPS), they might have survived. To achieve this goal, one would have to identify, among the variables available at clinical presentation, those predicting failure to control bleeding. An attempt at identifying such prognostic indicators was made in the training set of D'Amico's study [8]. At multivariable analysis, five parameters emerged as independent predictors of failure to control bleeding at day 5: presence of active bleeding at endoscopy, hematocrit, high aspartate aminotransferase levels, Child-Pugh class, and the presence of portal vein thrombosis. A prognostic model based on these variables was developed. A second analysis including the early follow-up variables (bleeding duration >12 h, bleeding duration >24 h, units of blood transfused at 24 h, total number of blood transfused and rebleeding) was carried out. Among the early follow-up variables, only the number of blood units transfused within 24 h was significantly related to 5 days failure. The second prognostic model included four variables: number of blood units transfused within 24 h, high aspartate aminotransferase levels, Child-Pugh class and the presence of portal vein thrombosis. The validity of both models was evaluated on the test set and showed a fair to good reproducibility (overall c statistic = 0.78 for both models), suggesting that patients at risk of failure to control bleeding and of early rebleeding can be identified with a reasonable degree of accuracy. In recent years, other studies have addressed the issue of the early identification of patients at high risk of failure to control bleeding and death. Abraldes et al. [21] published a study on 117 cirrhotic

patients with acute variceal hemorrhage treated with a combination of endoscopic and pharmacological therapy plus antibiotics, and analyzed several variables as predictors of 5-day treatment failure (a composite endpoint including failure to control bleeding, rebleeding, and death within 5 days). Failure occurred in 18 patients (15 %). Independent predictors of failure were an HVPG ≥ 20 mmHg, systolic blood pressure <100 mmHg at admission, and nonalcoholic etiology of cirrhosis. Since routine measurement of the HVPG is not feasible in most centers, they repeated the analysis including only clinical parameters: they found that Child-Pugh class, systolic blood pressure <100 mmHg at admission, and nonalcoholic etiology of cirrhosis predicted failure with a good degree of accuracy. Amitrano et al. [22] studied 185 cirrhotic patients with acute variceal bleeding treated with somatostatin, antibiotics and endoscopic band ligation; failure to control bleeding occurred in six patients (3.2 %), while eight patients (4.3 %) had variceal rebleeding within 5 days; mortality was 50 % and 62.5 %, respectively. By logistic regression analysis, Child-Pugh score, white blood cell count and the presence of portal vein thrombosis were identified as independent predictors of 5-day treatment failure.

In conclusion, patients at high risk for failure of first-line treatment, who should be treated more aggressively from the outset, can be identified by careful evaluation of clinical and endoscopic parameters at admission. These parameters are related to the severity of the underlying liver disease (Child Class, aspartate aminotransferase levels), to the severity of bleeding (active bleeding at endoscopy, number of blood units transfused at 24 h, systolic blood pressure), and to specific features of liver disease (portal vein thrombosis, nonalcoholic etiology of cirrhosis). Monitoring the early evolution of the clinical situation can also help making the decision to change to more aggressive treatments. Interestingly, this policy has been recently adopted successfully in a multicenter European trial [23].

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Chapter 5
Prevention of the Formation and Growth of Esophageal Varices

Carlo Merkel and Sara Montagnese

Why Varices Develop and Grow

Portal hypertension is a progressive condition, and most patients with cirrhosis eventually develop it [1]. The progressive increase in portal pressure is a consequence of the increase in intrahepatic resistance to portal blood flow (both in relation to anatomical changes and to active vasoconstriction), and subsequently the increase in splanchnic blood inflow due to splanchnic arterial vasodilation. The increase in portal pressure leads to the opening of small venous–venous channels which connect the portal vascular bed to the systemic circulation. An active de novo formation of vascular venous channels has also been demonstrated to play a role in the formation of the collateral circulation [2]. The formation of a vast collateral circulation, causing an expansion of the overall venous vascular bed, is the basis for the increase in plasma volume and cardiac output, leading to the hyperdynamic circulation which is observed in advanced cirrhosis, and which contributes to the development of further clinical complications.

Collateral circulation occurring in patients with intrahepatic portal hypertension is spread over different vascular regions, including the gastroesophageal, splenorenal, hemorrhoidal, umbilical, and paraumbilical systems. Less important systems are those qualified as accessory portal veins (Sappey's veins, connecting peripheral portal branches of the left liver lobe with the lower part of the falciform ligament), and Retzius system (connecting the intestinal veins with the inferior vena cava and its retroperitoneal branches). The amount of blood that is shunted through the collateral circulation may be considerable. The measurement of the azygos blood flow,

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which in patients with portal hypertension is an estimate of the blood flow through the gastroesophageal collateral circulation, documents values ranging from 0.3 to 2 L per minute in patients with advanced cirrhosis [3, 4]. It is reasonable to expect that flow may be similar in other collateral circulations, in particular the splenorenal collaterals, which are often documented by ultrasound examination, and are sometimes associated with the occurrence of overt hepatic encephalopathy [5].

At the gastroesophageal junction, the left gastric vein is connected with small veins within the adventitia of the esophagus, and the blood coming from the portal system and the left gastric vein, with reverse flow, drains in these small adventitial veins. In turn, they drain into the azygos and hemi-azigous, eventually feeding the superior vena cava. However, this system is insufficient for the incoming blood, and an expansion of the system occurs, with dilation of the intra-esophageal plexus, the perforating veins, and the mucosal plexus. The dilation of the mucosal plexus, the low pressure within the esophageal lumen, the hollow conformation of the organ, and the softness of the tissue surrounding the veins themselves, lead to the formation of esophageal varices. However, it should be remembered that varices are only a small part of the collateral circulation flowing through the gastroesophageal collateral circulation, and most of the blood flows through channels that cannot be seen on endoscopy. For these reasons, the observation of esophageal varices is a very specific indicator of the presence of portal hypertension—it being exceptional that a patient may show varices for reasons other than portal hypertension—but it is not a sensitive indicator, since a patient with portal hypertension may not have varices because the increase in portal pressure is very recent and varices have not yet developed, because portal pressure is increased to a lesser extent than that required for varices formation or because collateral circulation other than esophageal varices has developed.

Indeed, contrasting evidence of collateral circulations in different districts has been reported in the few studies addressing this issue. The comparison of collateral circulation documented on peritoneoscopy and on esophageal endoscopy (classified as absent, mild, or severe in each district) revealed agreement only in 63 % of cases, while the absence of esophageal varices in the presence of peritoneal collaterals was seen in 7 % of cases, and the absence of peritoneal collaterals in the presence of esophageal endoscopy varices in 2 % [6]. More recently, in a comparison of esophageal varices seen on endoscopy and ultrasound detection of paraumbilical collateral circulation, it was reported that the patency of the paraumbilical vein occurred with the same frequency in patients with and without esophageal varices (32/108–30 % and 15/35–43 %, respectively) [7]. This implies that anatomical factors may be responsible for the preferential development of collateral circulation in different areas, and that they are poorly predictable on a single patient basis.

It was suggested [8] that the presence of a patent paraumbilical vein, being a collateral circulation that does not feed the esophageal varices, may have a protective role in relation to variceal rupture. However, in a prospective study [9], the rate of formation/progression of esophageal varices was comparable in patients with and without patent paraumbilical vein. This observation is consistent with the concept that abdominal collaterals of any kind are an indication that the patient has gone a

further step in the natural history of the disease, which progresses accordingly. This is also confirmed by the observation that in patients whose collateral circulation increases on ultrasound during the follow-up, there is also a higher rate of progression of esophageal varices.

Prevention of Varices Formation

The prevention of the formation of esophageal varices would be a relevant clinical objective, since this would abolish the risk of bleeding. A prevention strategy would also be reasonable, since the formation of varices is a very frequent event in the course of the disease.

Since the formation of varices is the consequence of portal hypertension, and portal hypertension is the consequence of extensive liver fibrosis and of the splanchnic hemodynamic alterations which are typical of cirrhosis, it is obvious that therapeutic strategies aimed at containing fibrosis and preventing the occurrence of cirrhosis might be considered a form of prevention of variceal formation. Indeed, it has been shown that treatment of hepatitis B or C in patients with initial cirrhosis without varices may revert the disease, or at least prevent its worsening, thus decreasing the risk of portal hypertension-related complications, including the formation of varices [10, 11].

However, it may also be useful to prevent the aggravation of portal hypertension that is the cause of both varices formation, and the other portal hypertension-related complications. In consideration of the difficulties in performing long-term intervention studies in patients without a clinically relevant condition, so far only one trial on the prevention of varices formation has been performed [12]. This was a multicenter double-blind study in 213 patients with documented cirrhosis, portal hypertension defined as HVPG $\geq$6 mmHg, without esophageal or gastric varices on endoscopy, aimed at comparing the occurrence of varices in patients treated with a nonselective beta-blocker (timolol) or placebo. Patients randomized to timolol showed a significant decrease in HVPG, but the percentage of patients who did not reach the primary end-point (formation of varices or variceal bleeding) was nearly identical in the two groups. This disappointing conclusion was interpreted as indicating that, in this kind of patients, the pathophysiological mechanisms leading to portal hypertension (hyperdynamic circulation and increase in portal inflow) were weakly operating, and that nonselective beta-blockers might have been ineffective because of the lack of their main target. An alternative explanation is that the effect might have been too small to be demonstrated based on the size of the study and the length of follow-up, since during the study nearly half of the patients were withdrawn from treatment/decreased the dose, and 20 % were non-compliant. No further trial has addressed this issue, and it is unlikely that this might happen in the near future. Based on the available evidence, all clinical practice guidelines [13, 14] agree that beta-blockers cannot be recommended to prevent the formation of esophageal varices.

Prevention of Varices Growth

A very large spectrum of risk of variceal bleeding has been demonstrated in patients with cirrhosis and esophageal varices. Available predictive indexes agree that the size of varices, the presence of red wale marks, and the severity of liver dysfunction are the most important predictive factors [15–17] since bleeding is related to the increase in the esophageal wall tension (Fig. 5.1). According to the most popular predictive score, the NIEC index [15], the 1-year risk of bleeding may vary from 6 (small varices without RWM, compensated cirrhosis) to 76 % (large varices with RWM in patients with Child Class C). All intermediate values are possible. Thus, any clear distinction between patients with low-risk (small) and high-risk (large) varices is arbitrary. In general, varices are qualified as "small" if they are smaller than 5 mm, or F1 according to the Beppu's classification [18], or occupying less than 25 % of the esophageal lumen according to the ILCP classification [19].

Patients with small varices generally have lower HVPG than patients with large varices, the difference being significant only in some series [6, 20–22]. The overall risk of a first variceal bleed in untreated patients is around half of that of patients with large varices, but it is not negligible (approximately 10 % at 2 years) [15, 23–25]. Nonselective beta-blockers decrease portal pressure in patients with small varices to the same extent as they do in patients with large varices [26]. Thus, patients with small varices bear a quantitative rather than a qualitative difference compared to those with large varices and represent an earlier stage of the same pathophysiological condition.

It is clearly established and common clinical practice that patients with large esophageal varices should undergo prophylaxis of variceal bleeding either with beta-blockers or endoscopic band ligation. The case of patients with small varices is less clearly defined. Treating patients with small varices may be useful if the increase in size of the varices, which is associated with an increased risk of

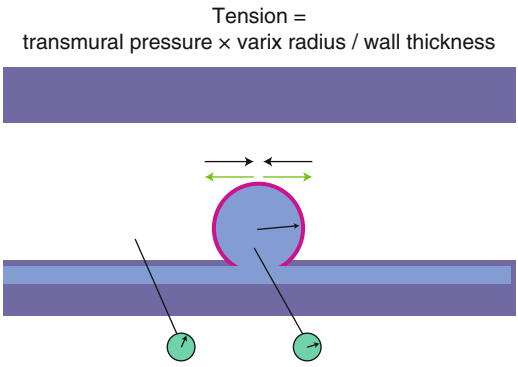

Fig. 5.1 A schematic drawing of the mechanisms involved in the wall tension of esophageal varices. The wall tension is the force (*black arrows*) that contrasts the tendency to expansion of the esophageal varix

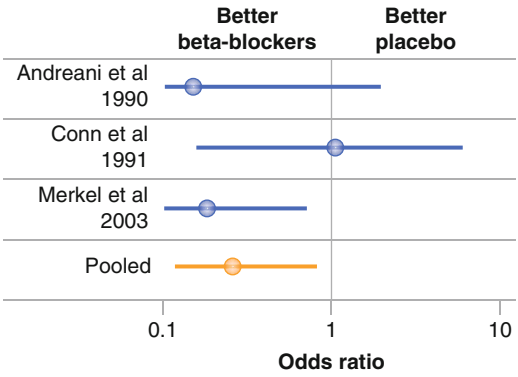

Fig. 5.2 Meta-analysis of the effect of beta-blockers vs. placebo in the prevention of first variceal bleeding in patients with small varices

bleeding, can be delayed; in this way, a decrease in bleeding risk should ensue. In addition, treating patients with small varices abolishes the need for endoscopic surveillance which is required to recognize the aggravation/increase in size of varices, and the consequent change in treatment strategy. Since surveillance strategies generally imply an annual follow-up endoscopy, and compliance is often suboptimal, starting treatment of small varices should be helpful in decreasing the risk of bleeding over the period of time between the aggravation of varices and its endoscopic demonstration.

For these reasons, a few years ago we performed a randomized controlled trial aimed at assessing if treatment with the beta-blocker nadolol in patients with cirrhosis and small esophageal varices delays variceal growth from small to large and decreases the risk of variceal bleeding [26]. Eighty-three patients were randomized to nadolol and 78 to placebo; patients were followed for up to 60 months. Patients randomized to nadolol exhibited a decrease in the risk of growth of esophageal varices (absolute risk difference: 30 %), and a decrease in the risk of variceal bleeding (absolute risk difference: 10 %). It was concluded that it is reasonable to start prophylaxis with nonselective beta-blockers in patients with small esophageal varices. No further trial has been performed to date, and comparative data can only be obtained by subgroup analyses of patients with small varices included in two trials of patients with large and small varices (mostly with large varices) treated with propranolol or placebo [27, 28]. A meta-analysis of these data showed a significant benefit of beta-blockers vs. placebo in the prophylaxis of the first variceal bleeding in patients with small varices (Odds ratio 0.32; 95 % CI 0.12–0.87) [29] (Fig. 5.2). However, given the limited amount of available data, practice guidelines are cautious, and report that such patients may (or should) be treated with beta-blockers, but further studies are required to confirm their benefit.

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Chapter 6
Beta-Blockers for All … or Not

Laure Elkrief and Didier Lebrec

Introduction

Since the first publication in 1980, nonselective beta-blockers have been extensively used in patients with cirrhosis and portal hypertension. The advantages of beta-blocker therapy are (a) good tolerance, (b) simple oral administration, and (c) low cost. In addition to their protective effect against variceal bleeding, it has been suggested that beta-blockers may decrease bacterial translocation. Because bacterial translocation is associated with the major complications of cirrhosis, beta-blockers could be prescribed as preventive treatment to all patients with cirrhosis. However, despite their advantages, the indication of beta-blockers should be limited to patients with a high risk of variceal bleeding. Indeed, clinical trials have not confirmed the efficacy of beta-blockers in patients who are not at a high risk of variceal bleeding. Side effects should also be taken into account by clinicians when deciding to prescribe beta-blocker therapy. Although side effects are frequent, and mainly minor, they affect the quality of life and are a major cause of poor compliance. This review discusses contraindications to beta-blockers, including general contraindications, which are not specific to patients with cirrhosis, but also cirrhosis-related contraindications, in particular portopulmonary hypertension and refractory ascites.

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Pathophysiology of Portal Hypertension and Rationale for Using Beta-Blockers in Patients with Cirrhosis

In cirrhosis, portal pressure initially increases due to increased resistance to blood flow, mostly because of architectural modifications in the liver secondary to fibrous tissue and regenerative nodules. Besides the structural resistance to blood flow, active intrahepatic vasoconstriction accounts for 20–30 % of the increased intrahepatic resistance [1], mostly due to a decrease in the endogenous production of nitric oxide [2]. Despite the development of portosystemic collaterals, portal hypertension persists, mostly due to an increase in portal territory blood flow from the concomitant development of splanchnic arteriolar vasodilatation [3, 4]. Therefore, the increase in portal pressure is a result of both an increase in resistance to portal blood flow and an increase in portal territory blood flow. Nonselective beta-blockers reduce portal pressure by reducing portal territory blood flow as a result of a decrease in cardiac output (β1-adrenergic blockade) and splanchnic blood flow (β2-adrenergic blockade) [5]. The decrease in portal pressure is mainly due to β2-adrenergic blockade, which explains why nonselective beta-blockers are more effective on portal pressure than cardioselective beta-blockers. The two beta-blockers that have been studied in patients with cirrhosis are nadolol and propranolol. Because portal hypertension is a basis for most of the clinical complications of cirrhosis, there is a clear pathophysiological rationale for using these drugs for this disease.

Indications of Beta-Blockers in Patients with Cirrhosis

Beta-Blockers in Patients Without Varices: Pre-primary Prophylaxis

Pre-primary prophylaxis is the term describing the use of beta-blockers to prevent the development of esophageal varices in patients with portal hypertension but without esophageal varices. The risk of developing varices depends upon the degree of portal hypertension: a baseline hepatic venous pressure gradient (HVPG) value above 10 mm Hg is the most powerful predictor of variceal formation [6]. The annual incidence of esophageal varices varies between 3 and 23 % [7, 8].

Beta-blockers have been shown to reduce portal pressure in patients with cirrhosis and limit the development of portosystemic shunts in portal hypertensive animals [9, 10]. For these reasons, three controlled studies have evaluated the usefulness of beta-blockers in preventing the development, or the growth of varices [11–13]. In the first study, Calès et al. performed a randomized double-blind trial in 206 patients with cirrhosis (mostly alcohol-related) without or with small varices to evaluate propranolol in the prevention of the development of large esophageal varices [11]. After 2 years the proportion of patients with large varices was higher in the

propranolol group than in the placebo group (31 % vs. 14 %, $P<0.05$). In the second study, 161 patients with cirrhosis with small varices and without previous bleeding were included [12]. Patients received either nadolol or placebo. After a mean follow-up of 3 years, the cumulative risk of developing large varices was 20 % in the treatment group vs. 51 % in the placebo group ($P<0.01$) [12]. In the third study Groszmann et al. included 213 patients with cirrhosis and no varices in a multicenter randomized controlled trial [13]. Forty percent of patients had an HVPG between 6 and 10 mm Hg, and 60 % had an HVPG above 10 mm Hg. In that study, patients received either timolol or placebo. Treatment with timolol did not prevent the formation of varices. However, the development of varices was less frequent in patients with a baseline HVPG <10 mm Hg and in those with a decrease in HVPG ≥10 % at 1 year. Treatment with timolol was associated with a high rate of adverse events, requiring a dose reduction or withdrawal in 50 % of patients [13].

Besides preventing varices, it has been suggested that beta-blockers could prevent the other complications of cirrhosis by reducing portal pressure. Indeed, some studies have found that HVPG above 10 mm Hg was an independent predictor of decompensated cirrhosis [14]. Moreover certain studies have found that beta-blockers decreased bacterial translocation in cirrhosis, which plays a key role in the complications of portal hypertension [15]. A meta-analysis found that beta-blockers participated in preventing spontaneous bacterial peritonitis [16]. Although these findings suggest that the administration of beta-blockers could prevent other complications of portal hypertension, in the trial performed by Groszmann et al. [13], the incidence of the complications of cirrhosis was the same in the patients treated by beta-blockers (timolol) and those receiving placebo.

These results suggest that beta-blockers may be useful in patients with small varices, and in those with HVPG >10 mm Hg to prevent the progression of varices as well as other complications of portal hypertension.

In conclusion, there are insufficient data to recommend beta-blockers in patients without or with small varices.

Primary Prophylaxis of Variceal Bleeding

A meta-analysis of 11 trials including nearly 1,200 patients and evaluating beta-blockers (propranolol or nadolol) in the primary prophylaxis of variceal hemorrhage showed that the risk of first variceal bleeding in patients with medium or large varices is significantly lower in patients treated with beta-blockers (14 % in patients treated with NSBBs vs. 30 % in controls) [17]. One bleeding episode is avoided for every ten patients treated. Mortality was also lower in the beta-blocker group than in the control group. It is important to note that beta-blockers reduced bleeding and bleeding-related mortality independent of variceal size, etiology of cirrhosis, the presence of ascites, or the severity of cirrhosis.

The mean rate of bleeding in patients with varices is 25 % after 2 years [18]. However, the risk of bleeding varies, and identifying patients at a high risk is important for the selection of candidates for prophylaxis. The risk of bleeding depends on the size of varices, the presence of red signs on varices, and the severity of liver disease. In patients with compensated cirrhosis (Child–Pugh class A) and small varices without red signs, the risk of bleeding is 6 %, while in patients with Child–Pugh class C cirrhosis, large varices and red signs, the risk of bleeding is 76 % [19]. The HVPG has also been described as a strong predictor of esophageal varices and variceal bleeding. Indeed, when the HVPG is below 10 or 12 mm Hg, the risk of developing varices at risk of bleeding is low [13, 20]. In a study including 100 patients with alcoholic cirrhosis, there were no relationship between the HVPG, the size of varices, and the occurrence of bleeding. In that study, the risk of gastrointestinal bleeding was significantly higher in patients with large varices than in those with no visible or with small esophageal varices [6]. Moreover certain patients with clinically significant portal hypertension (HVPG above 10–12 mm Hg) do not have varices [20].

In conclusion, primary prophylaxis with beta-blockers is not recommended in patients without varices, whatever the HVPG value.

Secondary Prophylaxis of Variceal Bleeding

Patients who survive an episode of acute variceal hemorrhage have a very high risk of rebleeding and death. The median rebleeding rate in untreated individuals is around 60 % after 1–2 years, with a mortality of 20–50 % [17, 21]. The first indication confirmed for beta-blockers was secondary prophylaxis [22]. Overall beta-blockers reduce the rate of variceal rebleeding from 60 % to approximately 40 % [21]. This rate decreases further when beta-blockers are combined with endoscopic band ligation. In two randomized trials, rebleeding rates were 23 % [23] and 14 % [24], respectively, for endoscopic band ligation plus beta-blockers (nadolol in these trials). These findings indicate that beta-blockers are effective in preventing recurrent bleeding Treatment combining beta-blockers to band ligation is more effective in the secondary prophylaxis of gastrointestinal bleeding [25].

In conclusion, beta-blockers may be recommended in all patients who have bled from varices.

Are Beta-Blockers Effective in All Patients?

In patients with portal hypertension the hemodynamic response to beta-blockers has been extensively studied [21]. However, the relationship between the hemodynamic response, adrenergic blockade, and the risk of variceal bleeding has not

been clearly demonstrated. The administration of beta-blockers can decrease the HVPG by 0–40 %. A hemodynamic response to nonselective beta-blockers is defined as a decrease in the HVPG of 20 % or to an HVPG value below 12 mm Hg. Long-term hemodynamic studies have shown that patients have a lower risk of variceal bleeding if the HVPG is below the 12 mm Hg threshold. Moreover, several studies have shown that if the HVPG is reduced by 20 % from baseline by drug therapy, even if it is not below 12 mm Hg, the residual risk of variceal bleeding is low [21]. Adrenergic response has been defined as a decrease in the heart rate of 25 %. It is important that the heart rate be measured 12 h after drug administration (or 24 h for long-acting beta-blockers) because a reduction in heart rate is always observed 1 or 2 h after drug administration. In addition the exercise test is a reliable method to assess beta-adrenergic blockade in patients with cirrhosis [26]. There is no relationship between the dose of beta-blockers and the intensity of blockade. Indeed, propranolol is metabolized by cytochrome P450 enzymes, which are characterized by a large interindividual and ethnical variability [27]. There is no correlation between the drug dose and hemodynamic response to propranolol [28]. In one prospective study, the results showed that the lack of persistent decrease in heart rate was an independent predictor of recurrent bleeding [29]. In relation to the association between hemodynamic response and the risk of bleeding, certain studies have found that the risk of bleeding was lower in hemodynamic responders [30] while others found that reduction in HVPG had no predictive value in evaluating the risk of recurrent bleeding [31, 32]. These conflicting results can be explained by confounding factors that influence HVPG such as alcohol abstinence, other treatment or co-existing infections at the time of hemodynamic measurements.

In conclusion, beta-blockers may be not effective in preventing gastrointestinal bleeding in hemodynamic "non-responders." A persistent decrease in heart rate after administration of non-selective beta blockers that does not increase after exercise identifies responders. Beta-blockers should not be used in non compliant patients.

The Side Effects of Beta-Blockers

Although they are usually not severe, the side effects of beta-blocker therapy must be taken into account. Indeed, Poynard et al. found that lack of compliance to beta-blockers was associated with recurrent bleeding [29]. In addition, a randomized trial showed that the risk of bleeding recurs when treatment with beta-blockers is stopped [33]. In patients with side effects, there is a greater risk of lack of compliance and treatment interruption. The most frequent side effects reported in patients treated for arterial hypertension were shortness of breath, tiredness, depressed mood, early awakening, and nightmares [34]. These have a negative influence on quality of life. The most common side effects with beta-blockers in cirrhosis are lightheadedness, fatigue, and shortness of breath. Although some of these side effects disappear over time or after dose reduction, treatment withdrawal occurs in 15 % of patients. The incidence of side effects differs from between 10 and 45 % [35].

Trials with nadolol reported lower rates of side effects (less than 10 %) than those with propranolol [36]. Side effects led to treatment withdrawal in 30 % of patients [29, 35].

In conclusion, compliance to beta-blockers should be carefully controlled in patients with mild side-effects to beta-blockers.

Contraindications to Beta-Blockers

General Contraindications

Most classical contraindications to beta-blockers are historical and are supported by evidence-based studies. Absolute cardiac contraindications are congestive heart failure and advanced heart blocks with severe bradycardia (Table 6.1). However, in patients with heart failure, beta-blockers are contraindicated in acute disease such as cardiogenic shock, but are effective in chronic heart failure [37]. Pulmonary contraindications include severe asthma and chronic obstructive pulmonary disease. However, the use of beta-blockers is safe in patients with moderate reversible airway disease [38]. Beta-blockers are also normally contraindicated in patients with peripheral vascular diseases, such as Raynaud disease and peripheral arterial disease. Although a meta-analysis found that beta-blockers did not influence intermittent claudication, these studies were performed with cardioselective beta-blockers [39]. Beta-blockers may worsen hypoglycemic episodes, leading to loss of consciousness in diabetic patients receiving insulin treatment. However, a study comparing subjects with diabetes who were receiving beta-blockers or not found that beta-blockers did not increase the number or the severity of hypoglycemic episodes [40].

In conclusion, most of the general contraindications are relative, and beta-blocker therapy is safe in most cases.

Table 6.1 General and cirrhosis-related beta-blockers contraindications

General contraindications		Cirrhosis-related contraindications
Absolute	Relative	
Severe congestive heart failure	Moderate chronic heart failure	Portopulmonary hypertension
Advanced heart block	Asthma	Refractory ascites
	Chronic obstructive pulmonary disease	
	Peripheral arterial disease	
	Raynaud disease	
	Insulin-treated diabetes mellitus	

Cirrhosis-Related Contraindications

Portopulmonary Hypertension

Portal hypertension is known to be a predisposing factor for the development of pulmonary arterial hypertension (portopulmonary hypertension), and occurs in 6–8 % of patients with cirrhosis [41]. Portopulmonary hypertension, is hemodynamically defined as a mean pulmonary arterial pressure >25 mm Hg and pulmonary vascular resistance >240 dyn.s.cm^{-5}, with a pulmonary artery occlusion pressure <15 mm Hg [42]. Patients have extensive pulmonary vascular remodelling (leading to increased vascular resistance) which can lead to right heart failure. However, the presentation of portopulmonary hypertension varies. Patients can be either asymptomatic or present with dyspnea. The diagnosis of portopulmonary hypertension may be suspected during echocardiogram screening [43] (showing elevated right atrial pressure and/or tricuspid regurgitation), but must be confirmed hemodynamically by right heart catheterization. One study has shown that beta-blockers were deleterious in patients with portopulmonary hypertension [44]. Indeed a 6-min walking test and cardiac output improved significantly 2 months after the withdrawal of beta-blockers.

> In conclusion, beta-blockers should not be used in patients with portopulmonary hypertension. Thus systematic screening for portopulmonary hypertension should be performed before beginning beta-blockers in patients with cirrhosis.

Patients with Severe Cirrhosis

A recent prospective observational study in 151 patients with cirrhosis and refractory ascites found that beta-blockers were significantly associated with poorer survival [45]. One year later the same authors published a self-control cross-over study in ten patients with refractory ascites treated with beta-blockers. They found that after beta-blockers were discontinued, heart rate immediately increased following paracentesis (while it did not in patients treated with beta-blockers), and paracentesis-induced circulatory dysfunction occurred in only one patient (while it occurred in eight patients receiving beta-blockers) [46]. These results suggest that beta-blockers increase the risk of paracentesis-induced circulatory dysfunction in patients with refractory ascites and thus should be contraindicated. Certain authors have also suggested that the deleterious effect of beta-blockers on survival was due to a reduction in cardiac output [47] because low cardiac output has been associated with a poor outcome and the development of the hepatorenal syndrome [48]. However, a retrospective study in 68 patients with cirrhosis admitted to the intensive care unit for severe infection found that beta-blockers had no effect on outcome, suggesting that the underlying mechanisms of their effect on survival is not due to an inadequate hemodynamic response to severe sepsis [49]. Calès et al. found that in patients with

alcoholic cirrhosis, survival was poorer in patients with a MELD score ≥12 treated with beta-blockers (although this was not significant) than in patients without beta-blockers. On the contrary, survival was better in patients with a MELD score <12 receiving beta-blockers [50].

In conclusion, beta-blockers should be avoided in patients with cirrhosis and refractory ascites. Beta-blockers may also be deleterious to patients with severe cirrhosis.

Summary

Please see Fig. 6.1 for the proposed indications and contraindications of beta-blockers therapy in patients with cirrhosis.

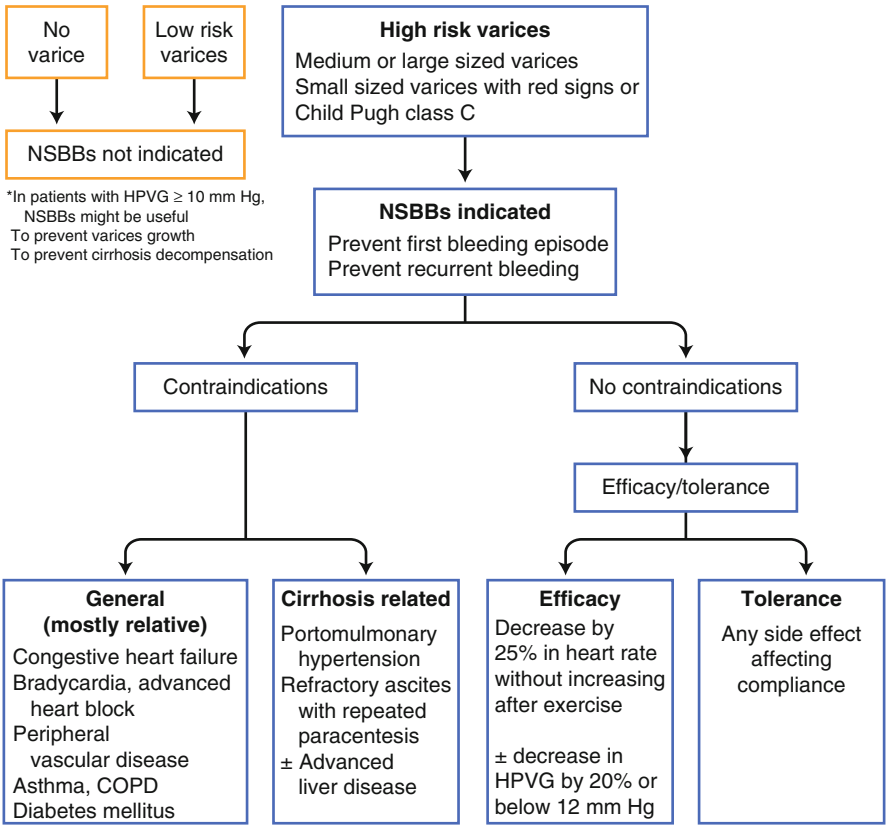

Fig. 6.1 Proposed indication and contraindications of beta-blockers therapy in patients with cirrhosis. (*COPD* chronic pulmonary obstructive disease, *HVPG* hepatic venous pressure gradient)

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Chapter 7
Pre-primary and Primary Prophylaxis of Variceal Hemorrhage

Tilman Sauerbruch and Jonel Trebicka

Introduction

Variceal hemorrhage is a life-threatening complication of portal hypertension. Depending on the degree of liver decompensation mortality averages around 20 % [1]. In our own studies, we found an esophageal variceal bleeding-related death rate of nearly 40 % [2, 3], although in-hospital death rate of variceal bleeding has dropped considerably within the last decades [1]. However, a rather high percentage of patients still die before they are admitted. Hence, despite the fact that bleeding is no longer the most frequent complication of liver cirrhosis, preventing bleeding from varices induced by portal hypertension remains a major treatment aim. The natural history of liver cirrhosis induced by chronic viral infection [4] shows an occurrence rate of ascites and hepatocellular carcinoma of around 2 % per year after diagnosis of compensated liver cirrhosis, while variceal bleeding occurred only in 5 % of patients within a time period of 10 years. Furthermore, bleeding is often more a bystander than a cause of severe liver decompensation. Nevertheless, variceal bleeding is a dramatic event and clinicians have been developing strategies for its treatment and prevention over decades.

This chapter reviews the main achievements and delineates new approaches to avoid first variceal bleeding which includes prevention of variceal formation.

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Pathogenesis of Varices and Bleeding

The driving force for the formation of varices is portal hypertension [5] associated with hampered flow of the portal venous blood to the inferior caval vein. This induces formation of collaterals to drain the blood to the right heart, mainly via the superior vena cava. Portal hypertension is defined as portal pressure, which exceeds the pressure in the vena cava by more than 5 mmHg [6]. It is commonly assumed that varices develop once this pressure surpasses 10 mmHg; a pressure threshold established as significant portal hypertension. If this pressure is higher than 12 mmHg, esophageal varices may rupture and bleed [5, 6]. Most bleedings are intestinal, namely from esophageal varices and gastric varices, while large collaterals embedded in the paraintestinal tissue very rarely show spontaneous rupture.

At the distal part of the esophagus, the varices are only covered by a thin epithelial layer and often not by the muscularis mucosae [7, 8]. Furthermore, the transmural pressure gradient augments in the thoracic segments of the collaterals, where the luminal pressure is lower than in the abdomen [9]. This may explain why the region of the gastroesophageal junction or just above the lower esophageal sphincter is critical for the occurrence of bleeding.

Risk Factors and Prognostic Signs

According to La Place's law, tension of the wall is proportional to the radius of the vessel multiplicated the transmural pressure, whereas it is inversely related to the thickness of the wall [10, 11]. This law can only partially be adapted to the situation of venous collaterals in humans but it provides indications. Thus, hemodynamic factors such as the esophageal variceal blood pressure or—indirectly—the portal blood pressure on the one hand and morphological characteristics of the vessel, such as size and properties of the wall, on the other hand [7, 9] possibly deliver indications about the risk of bleeding and therewith prognostic information. Another intrinsic factor may be deranged blood coagulation, e.g., triggered by infection [12].

Several clinical situations can precipitate or augment these risk parameters.

Hemodynamic Parameters

The gradient of wedged hepatic venous pressure minus free hepatic venous pressure or minus the inferior vena cava pressure approximates the portal venous pressure measured directly [13]. In patients with previous variceal hemorrhage, this hepatic venous portal pressure gradient (HVPG) was nearly always greater than 12 mmHg. Yet, this pressure could in fact represent the threshold for formation of varices rather than serve as a good discriminator for bleeding, since many retrospective studies [14, 15] failed to find significant differences of the average HVPG between bleeders

and non-bleeders. Few data exist on the risk of diurnal pressure changes, e.g., induced by meals or physical activity, which can be quite remarkable [16]. Furthermore, portal flow may vary considerably between patients with a similar degree of portal hypertension.

There is some evidence that blood pressure within the varix or transmural pressure [17], which, however, is ideally assessed invasively, might be a better predictor of variceal bleeding [18].

The new technologies that determine liver stiffness noninvasively by measuring velocity of the propagation of vibration wave can quite accurately predict significant portal hypertension, i.e., HVPG >10 mmHg. Liver stiffness below 13.6 kPa rules out significant portal hypertension, while liver stiffness greater than 21.1 kPa is always associated with an HVPG above 10 mmHg [19]. Techniques to assess liver stiffness are increasingly integrated into ultrasound devices, and future equipments might allow estimation of portal blood flow, spleen size, diameter of the portal vein, as well as stiffness of the liver in one step. It remains to be seen whether these techniques will allow monitoring of the effect of drugs applied to lower portal pressure.

Morphological Features of the Vessels

Although transmural pressure is the driving force that causes rupture and bleeding, morphological alterations of the wall may well support this event. Local erosions resulting in a reduction of wall thickness can be a precipitating event in large varices with high wall tension [7, 9]. These alterations are sometimes evident during endoscopy as the so-called white clot [20].

Furthermore, typical features of varices include red color signs (red wale markings, hematocystic spots) or size of varices that allow the prediction of variceal pressure and risk of bleeding [21, 22]. These parameters are part of one of the most relevant prognostic scores applied to calculate the risk of bleeding and to define patients for prophylaxis of first bleeding [21, 23–25].

Blood Coagulation

Bleeding occurs more often in patients with decompensated cirrhosis independent of the macroscopic variceal characteristics. This may be partly due to an impaired coagulation following infections [12, 26].

Precipitating Events

For prophylaxis of variceal bleeding, exact knowledge of events triggering bleeding is important [9]. If size of varices, wall characteristics [22–25, 27], portal as well as transmural variceal pressure, alcoholism [21], and degree of liver dysfunction are

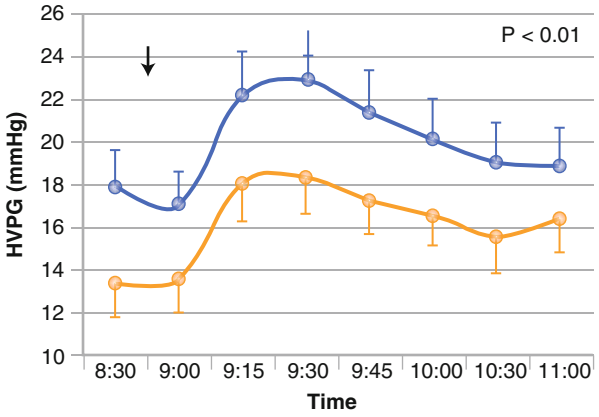

Fig. 7.1 Increase of the portal pressure after meal (*arrow*) as assessed by HVPG in 12 patients with liver cirrhosis (*blue circles*). Three-week treatment with propranolol (−25 % pulse rate, mean dosage 93 ± 13 mg) significantly decreased portal pressure, but did not influence increase after meal (*yellow circles*). (Used with permission from Schiedermaier P, Koch L, Stoffel-Wagner B, Layer G, Sauerbruch T. Effect of propranolol and depot lanreotide SR on postprandial and circadian portal haemodynamics in cirrhosis. Aliment Pharmacol Ther 2003;18:777–784)

predictive for first bleeding, events that aggravate these parameters must be triggers for bleeding. These might include a sustained rise of portal pressure, e.g., induced by infection, alcoholism, or acute activation of contractile cells within the liver derived from the gut or elsewhere (pulmonary, urinary infection, or other foci of infection). Short-term increase of portal pressure due to meals (Fig. 7.1) or abdominal pressing have not consistently been found to trigger bleeding [16]. Erosions of the thin walls of large vessels could also be a trigger, but—again—only very few studies consider gastroesophageal reflux a risk factor for portal hypertensive bleeding [26].

According to the previously mentioned studies, strategies for pre-primary and primary prophylaxis of variceal hemorrhage should aim to:

- Prevent formation of varices mainly by reduction of intrahepatic resistance or by prevention of its increase.
- Prevent growth of varices.
- Prevent precipitating events if large varices are present, e.g., by reducing pressure and flow within the varices, by preventing infections, acute alcohol challenge, or other factors that lead to deterioration of liver function.
- Improve wall characteristics and/or reduce size of the vessels.

Pre-primary prophylaxis concentrates mainly on modulation/reduction of intrahepatic resistance, while primary prophylaxis with its available therapeutic options focuses more on modulation of the splanchnic vascular bed (e.g., application of nonselective β-blockers) and on direct alteration of the vascular segments at risk for bleeding (e.g., obliteration of varices using ligation).

Pre-primary Prophylaxis

Patients with liver cirrhosis show esophageal varices in about 60 % of the individuals at the time of diagnosis [28]. In the remaining patients, the annual incidence of varices is about 7 % [28]. Although nonselective β-blockers are the standard treatment to prevent the first variceal bleeding, they have failed to retard the development of varices in cirrhotic patients [28, 29] despite encouraging experimental data [30].

Chronic liver disease is a result of a persisting hepatic injury with hepatocellular damage, inflammation, and fibrosis. During this process, many functional and structural changes, such as fibrosis, angiogenesis, hypocontractility of splanchnic vessels, and hyperreaction of contractile cells within the liver, take place and all contribute to the development of portal hypertension and formation of varices. The withdrawal of the underlying hepatic injury and different pharmacological approaches have been successfully tested in human and animal models to inhibit, attenuate, or reverse the processes associated with development of fibrosis, angiogenesis, or alterations of vascular responses. Since these processes interact during disease progression, a multimodal approach is preferred to offer new possibilities for future pre-primary prophylaxis.

Withdrawal of the Underlying Hepatic Injury

Until recently, established hepatic fibrosis was believed to be irreversible [31]. Today, however, many different studies show that elimination of the underlying cause may indeed reverse fibrosis and prevent the development of portal hypertension together with varices. Thus, different studies in patients with chronic viral hepatitis type B and C have shown that virus elimination leads to regression of fibrosis and cirrhosis [32–34], while other studies reported that drain of bile in chronic cholestasis ameliorated liver fibrosis as well as treatment of autoimmune hepatitis and weight loss in nonalcoholic steatohepatitis [35–37].

Antifibrotic Strategies

Although strategies to target the cause of the liver disease are mostly efficient, they may fail (e.g., treatment of chronic HCV infection or primary sclerosing cholangitis) or are initiated in a too advanced stage due to late diagnosis. In this situation, therapies that interrupt or attenuate fibrogenesis would be most helpful in order to decrease portal hypertension and its complications.

The key cells responsible for hepatic fibrosis are the hepatic stellate cells. They are activated and change their phenotype upon liver injury in that they transform towards cells that contract and produce extracellular matrix. Both phenomena

increase the intrahepatic resistance to portal flow. In the past, many approaches have been investigated in experimental models of fibrosis. Here, we focus on strategies that may be transferred to the human situation.

Activation of the Renin–Angiotensin System

The renin–angiotensin system (RAS) is increasingly activated with decompensation of liver cirrhosis, probably as a reaction to systemic vasodilation [38, 39], while at the same time, tissue RAS, especially within the liver, may stimulate hepatic stellate cells via angiotensin 1 (AT1) receptors inducing fibrosis, vasoconstriction, and portal hypertension [40, 41]. In the past, many drugs, which modulate RAS have been validated and are now part of clinical routine in cardiovascular disorders.

Similarly, it has been shown in animal models of liver fibrosis that angiotensin type 1 receptors (AT1R) are upregulated within the liver together with angiotensin II formation. Blockade of this cascade via angiotensin-converting enzyme (ACE) or preventing angiotensin II binding to AT1 receptors attenuates fibrosis and decreases portal pressure [42–45]. Chronic administration of these available drugs might therefore play a role in the pre-primary prophylaxis of variceal bleeding. However, randomized trials are lacking to date. Around 10 years ago, a homologue to ACE, the so-called ACE2, has been described [46]. ACE2 degrades the active angiotensin II to angiotensin 1–7, which binds to the so-called MAS receptor. This receptor elicits contrary effects to AT1Rmediated processes; it blunts fibrosis and causes vasodilation. Thus, ACE2-deficient mice show more severe liver fibrosis, while the administration of recombinant ACE2 reduces experimental liver fibrosis [47, 48] and reduces portal hypertension via the degradation of angiotensin II to angiotensin 1–7 by dual effect prevention of AT1R stimulation and increased MAS receptor stimulation. Modulation of this system could also play a future role in pre-primary prophylaxis of variceal bleeding.

Statins

HMG-CoA reductase inhibitors have effects that are independent from the lowering of serum cholesterol. These are mediated by the inhibition of the small GTPases [49–52]. Interestingly, statins decrease by this way accumulation of extracellular matrix within the liver, induce senescence in activated hepatic stellate cells and lead to relaxation of these cells (Fig. 7.2a–c) [49–52]. Such experimental data suggest an effect in the prevention and/or treatment of portal hypertension and thereby pre-primary prophylaxis of varices in chronic liver disease. As a proof of principle, it has already been shown in rather small studies that statins reduce portal pressure [53, 54] and possibly attenuate matrix formation [55–57]. Yet, again, large trials, especially regarding development of portal hypertension, are lacking.

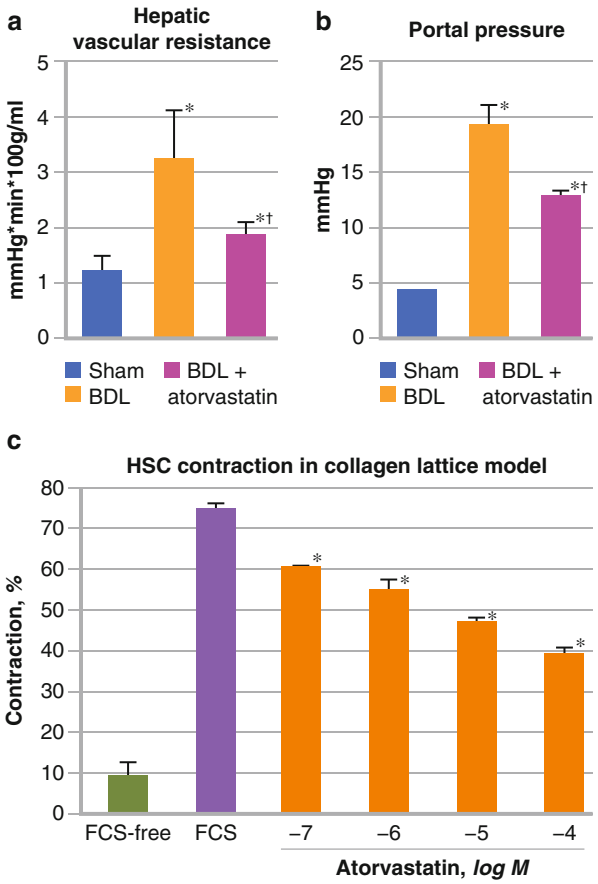

Fig. 7.2 (**a**–**c**) Effect of 1-week atorvastatin feeding in rats with biliary cirrhosis as compared to controls. Mainly due to reduction of the intrahepatic resistance (**a**) the portal pressure decreases (**b**). This effect is caused by relaxation of activated hepatic stellate cells as shown in the in vitro experiment (**c**). (Used with permission from Trebicka J, Hennenberg M, Laleman W, Shelest N, Biecker E, Schepke M, Nevens F, et al. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. Hepatology 2007;46:242–253)

Modulation of the Intestinal Microbiota

Liver cirrhosis is associated with small intestinal bacterial overgrowth, bacterial translocation, and change of the gut microbiota [58, 59]. All these factors can indirectly cause an increase in intrahepatic resistance (e.g., via activation of intrahepatic macrophages and hepatic stellate cells), hyperdynamic circulation and impairment of coagulation, derangements that may provoke portal hypertension and variceal

bleeding [60–63]. Thus, pathogen-free animals or those with interrupted pathways of innate immunity show considerably less hepatic fibrosis [64, 65]. Future will tell whether influencing intestinal microorganisms, the host immune response and the mucosal barrier will one day become a tool for the prophylaxis of variceal formation and variceal bleeding. A small trial showed that application of Rifaximin, a nonabsorbable antibiotic, indeed reduced portal pressure in humans [66].

Antiangiogenetic Approaches

Antiangiogenetic factors trigger and aggravate hepatic fibrogenesis [67] and it has been repeatedly shown, at least in animal models, that substances such as antibodies against vascular endothelial growth factor (VEGF) or tyrosine kinase inhibitors attenuate liver fibrosis [68–73]. Yet, as of today it remains open whether such strategies will translate into clinical hepatology for the prevention of varices.

Interestingly, angiogenesis also plays an important role in the de novo formation of portosystemic collaterals. Inhibition of angiogenesis in splanchnic vessels by inhibiting VEGF or PDGF resulted in the reduction of portal pressure and could possibly prevent the formation of varices [74–76]. One drug already used in clinical hepatology is sorafenib. Apart from its antiproliferative effect, it blunts angiogenesis as shown in portal hypertensive animals [71].

Modulation of Hepatic and Extrahepatic Contractile Cells

Portal hypertension is driven by the increased intrahepatic resistance—which is structural (fibrosis) and dynamic (intrahepatic activation of contractile cells)—and by an increased portal tributary blood flow resulting from splanchnic vasodilation [39, 77]. Both vessel beds are targets for drugs to prevent variceal bleeding or reverse portal hypertension.

Decreasing Hepatic Resistance

Different approaches have been shown to lower portal pressure via reduction of intrahepatic resistance. An important target is the deactivation of stimulated hepatic stellate cells, Kupffer cells, or liver sinusoidal endothelial cells to facilitate portavenous blood flow through the liver. Drugs that blunt the basic mechanisms of contraction, e.g., the RhoA/Rho-kinase pathway, or enhance the delivery of vasodilative molecules, such as nitric oxide, effectively reduce intrahepatic resistance and portal pressure [49, 78–80]. Drugs that have been successfully tested for efficacy in this situation include AT1R antagonists [44, 45, 81, 82], amiloride [83], nitroflurbiprofen [84], nitrates [77], statins [49, 53, 54, 85], β3-AR agonists [80], or MAS receptor agonists [86]. The following paragraphs will concentrate on clinical trials, which tested some of these drugs for prevention of variceal bleeding.

Unfortunately, medical treatments that reduce intrahepatic resistance may have considerable systemic side effects by further decreasing systemic arterial blood pressure and aggravating hyperdynamic circulation. Therefore, targeting specific cells within the liver might provide an answer. For example, a potent Rho-kinase inhibitor coupled to modified human serum albumin selectively decreased intrahepatic resistance without influencing systemic hemodynamics [87]. These molecules can also be used as a Trojan horse for the AT1R-blocker losartan [88].

Increasing Splanchnic Vascular Tone

Increase of the splanchnic vessels tone decreases portal pressure via reduction of the portal tributary blood flow. Several animal studies have shown that low-dose AT1R-blockers and urotensin II receptor antagonists lower portal pressure via an increase of splanchnic vascular resistance and a decrease in the portal blood flow [45, 81, 89, 90]. Further compounds, such as neuropeptide Y, multi-kinase inhibitors, and MAS receptor blockers, exhibit a portal pressure lowering effect via correcting the deranged vasocontratile pathways and increasing the splanchnic vascular tone [39, 72, 86, 91–93]. Yet, at present, all these approaches to prevent and treat portal hypertension are experimental with the exception of the application of some vasoconstrictors such as terlipressin [94, 95].

Primary Prophylaxis

Shunts, drugs, and endoscopic obliteration of varices prone to bleed have all been tested for prevention of first variceal hemorrhage in numerous clinical trials that are addressed in the following paragraphs.

Shunting Procedures

Four randomized controlled trials [96–99] were performed in the 1960s and early 1970s. Variceal bleeding was prevented by insertion of a surgical shunt in the vast majority of patients, while first bleeding ranged between 20 and 40 % in the non-shunted individuals. However, during a follow-up period of 5–14 years, 44 % of the non-operated and 58 % of the operated patients died. This excess mortality was mainly due to operative mortality and a higher long-term hepatic failure rate in the shunted patients.

Since then, the surgical shunt has been considered a sacrilege in the prophylaxis of first variceal bleeding. TIPS has a much lower procedure-related trauma and can be easily occluded, but to date, no controlled trials have been initiated to test the value of TIPS for primary bleeding prophylaxis, despite the fact that such an approach has some theoretical basis in selected candidates.

Local Treatment of Collaterals

In 1939, Crafoord and Frenckner introduced sclerotherapy of esophageal varices [100]. In the early 1980s, first trials were conducted that favored sclerotherapy with respect to bleeding and survival. Numerous further trials, however, were less clear-cut [3, 101] or even showed an excess of bleeding. A large meta-analysis of 19 trials considered sclerotherapy unsettled for the prevention of first bleeding [102]. The results were too heterogeneous, which was mainly due to a large variation of the bleeding incidence in the control groups, although pooled odds ratios were in favor of sclerotherapy. The largest trial even found a higher death rate in the group of patients treated with sclerotherapy [103].

Later on ligation was introduced [104] and showed to have less adverse effects, especially in respect to procedure-related bleedings. Five trials compared prophylactic ligation with untreated controls comprising 601 patients. A meta-analysis found a homogenous beneficial effect with respect to reduction of first variceal bleed, bleeding-related mortality, and all cause mortality. Consequently, ligation has become the endoscopic procedure of choice in the prevention of first variceal bleeding [105]. Typically, 2–3 sessions of ligation are necessary. The interval between these sessions varies between the groups from 1 to 3 weeks, with 2–3 weeks [106] as possibly the best interval for the repetition of the procedure. Although ligation has been shown to be effective for prophylaxis of first bleeding, it has to be kept in mind that the procedure depends on the experience of the endoscopist and that it may induce life-threatening bleeding [2].

Medical Treatment for Prophylaxis of First Bleeding

Nonselective β-Blockers

Portal hypertension is caused on the one hand by an increased intrahepatic resistance and on the other hand by an augmented portal tributary blood flow—as first shown by Didier Lebrec and his group [107]. It is believed that the latter phenomenon contributes about one third to the degree of portal hypertension. The speculation by the French group of Clichy that portal tributary blood flow could be reduced by administration of a nonselective β-blocker was indeed ingenious. The blockade of β1-adrenoceptors decreases the cardiac index and therewith the splanchnic inflow. At the same time, blockade of the β2-adrenoceptors renders α1-adrenergic reaction unopposed within the splanchnic vasculature, which results in vasoconstriction and a further drop in splanchnic perfusion [108]. The decreased splanchnic perfusion and consequently the reduced portal venous inflow achieve—on average—a reduction of portal pressure by 12 % [109, 110]. It is believed that it is mainly this long-term reduction of portal pressure under continuous intake of

propranolol that reduces the bleeding risk, as shown consistently in randomized controlled trials [111]. It was suggested early on that propranolol should be dosed up to a reduction of the heart rate by 25 % or the maximal tolerated dose. Once this hemodynamic reaction is achieved, 20–40 % of patients [109, 110] show a decrease of HVPG by ≥20 %, which is believed to be the best prognostic sign for prophylaxis success. An analysis of the data of 589 individual patients from four randomized trials [111] showed that the percentage of patients without upper gastrointestinal bleeding increased from 65 % (controls) to 78 % (verum groups) within 2 years. The percentage of patients without fatal bleeding increased from 82 % (controls) to 90 % (β-blocker). There was a trend in favor of prolonged survival, but this was far from being significant (71 % vs. 68 %, $p = 0.34$).

The previously mentioned results are robust and established the role of nonselective β-blockers as treatment of choice for prophylaxis of first bleeding in patients with liver cirrhosis and large esophageal varices [95]. One trial [29] showed that patients with small varices might also profit. However, pharmacological approach using nonselective β-blockers presents some problems. Five to ten percent of patients were non-compliant or non-adherent to treatment [112], 5% of patients exhibited contraindications such as hypotension, bradycardia, impotence, or dyspnea and in 10–25 % of patients [112], adverse events occurred that required interruption of treatment. Finally, β-blockers must be applied on a lifelong basis since the risk of variceal hemorrhage returns to the untreated situation after withdrawal of treatment [113].

Thus, in a rather high percentage of these patients, other approaches have to be considered, such as ligation, nitrates, or carvedilol, a nonselective β-blocker, which also blocks α-adrenergic receptors [114, 115]. The following paragraphs will address the controlled trials, which have been carried out with these different approaches to prevent first variceal bleeding in patients with liver cirrhosis and large varices.

Nitrates for Prevention of First Bleeding vs. Placebo

Vasodilators, especially long acting nitrovasodilators (e.g., isosorbide dinitrate or isosorbide mononitrate) have been shown to reduce HVPG [115, 116] and esophageal variceal pressure by reduction of vascular resistance to portal collateral blood flow and possibly also intrahepatic resistance [117]. One trial [118] with 133 patients compared isosorbide-5-mononitrate in a double blind randomized trial with placebo in patients with contraindications or intolerance to β-blockers. No difference was found in the 1 and 2 year actuarial probability of first variceal bleeding. In further studies, nitrates were inferior to propranolol [119–121] and ligation [119]. Accordingly, nitrates are not an alternative for propranolol to prevent first bleeding. Combining nitrates with a nonselective β-blocker for prophylaxis of first bleeding may have a small additional beneficial effect [122, 123].

Ligation vs. a Nonselective β-Blocker

To date, at least 19 randomized controlled trials (eight available only as abstracts) have been published. The conclusions of two recent meta-analyses [106, 124] are quite similar in that within a time period ranging between 10 and 55 months, all-cause mortality was nearly identical (23 % vs. 24 % out of approximately 1,500 patients in total) and that variceal ligation significantly reduced the bleeding risk when all trials are analyzed (11 % vs. 20 % nonselective β-blockers). This effect was rather robust but it is no longer significant when only high quality trials were included [106]. Adverse events occurred more often in the β-blocker groups, but fatal adverse events—caused by induction of bleeding—were only reported for the ligation groups (3 %) and not in the β-blocker groups.

Bleeding-related complications may be lower when the interval between banding sessions surpasses 2 weeks [106]. Compliance was inconsistently reported. In our own trial [2], 5 % of patients presented contraindications, 9 % did not adhere to β-blockers and in 16 %, β-blocker treatment had to be stopped mostly due to symptomatic arterial hypotension, which may cause "rebound bleeding" [113]. Higher doses of propranolol (>75 mg/day) were somewhat more efficient than lower doses, but only in the initial period of treatment [106].

Both meta-analyses concluded that it might be appropriate to start with a nonselective β-blocker and to restrict ligation to patients who have contraindications or do not tolerate β-blockers. However, if patients prefer ligation it appears appropriate to accept their wish. Beta-blockers may be particularly suitable for patients prior to liver transplantation [125].

While prophylaxis with nonselective β-blockers is less cost-intensive [2], this may change in favor of ligation once life quality is additionally considered [126].

Ligation Plus a Nonselective β-Blocker

Several singular trials addressed the question of combining different therapeutic principles for prophylaxis of first bleeding. Ligation was more effective than nadolol plus isosorbide-5-mononitrate for prevention of first bleeding [127], while adding propranolol to ligation did not improve the effect of ligation in the setting of primary prophylaxis [128]. Thus, contrary to prevention of rebleeding [95], combination therapy is obviously not superior when first variceal bleeding is to be prevented.

Carvedilol Instead of Propranolol

Carvedilol is a nonselective β-blocker with intrinsic anti-α1-adrenergic activity. Hemodynamic studies [109, 110, 129] showed that a daily dose of carvedilol of 12.5–25 mg reduces the average HVPG to a higher relative degree than propranolol (around 19 % vs. approximately 10 %). Accordingly, more patients are responders

(drop of HVPG >20 % or to <12 mmHg) with carvedilol when compared to propranolol (54 % and 23 %, respectively) [110], while somewhat more than 50 % of patients, who did not respond to propranolol, still showed an adequate response to carvedilol [109]. This renders carvedilol a potential treatment of choice for bleeding prophylaxis [130]. Yet, no controlled trial on the direct comparison to propranolol for primary prophylaxis has been published to date. Regarding head to head comparison with ligation in the setting of primary prophylaxis, one trial showed a significantly lower first bleeding rate [131] in the carvedilol group (10 %) compared to ligation (23 %), while another trial found no difference [132]. Survival was not different in either trial.

Although not found in all trials, a more pronounced reduction of the mean arterial pressure under carvedilol, especially in patients with decompensated cirrhosis, remains a concern [114], especially with respect to kidney function and treatment of ascites.

Thus, more trials must be published before carvedilol can be regarded as treatment of choice for the prevention of first bleeding from varices. Nevertheless, individual patients may already be candidates.

Fundic Varices

Coexisting gastric varices do not preclude prophylactic ligation of large esophageal varices [133]. Only one randomized trial evaluated primary prophylaxis for bleeding from large isolated gastric varices [134]. Nearly half of the untreated patients bled within 2 years. Cyanoacrylate injection significantly reduced this risk and was more successful than β-blockers.

Further Alternatives in the Pipeline

Drugs that are antifibrogenic [135] and—at the same time—reduce portal pressure would be ideal (see previous discussion). Here, blunting the activated RAS in liver cirrhosis could be an option as mentioned earlier. One study found a dramatic short-term effect of the AT-1-receptor blocker losartan (25 mg daily), which reduced HVPG by nearly 50 % [136]. Unfortunately, this finding could not be confirmed by further trials [81, 82]. Furthermore, dramatic hypotensive effects in patients with highly activated RAS and kidney failure may be a problem [81, 137]. However, in patients with well-compensated cirrhosis, this approach could be an option for long-term treatment if the dose is carefully titrated. This has been suggested by preclinical studies. In rat models of cirrhosis, low-dose administration of losartan could reduce portal pressure and improve vascular hypocontractility, and finally, renal function [45, 89]. While we found no additional effect when adding irbesartan to low-dose propranolol for reduction of HVPG, sodium excretion increased when we added the AT1-antagonist [138]. Spironolactone has also shown no additive effect

in bleeding prevention [139]. Long-term trials with relevant clinical endpoints, such as liver function/histology, bleeding, and survival, are certainly called for.

Somatostatin analogues, shown to reduce portal pressure in very early studies, are not an option for prevention of first variceal bleeding since their portal pressure lowering effect is minor or even absent [140, 141].

Other new drugs and strategies addressing fibrosis, angiogenesis, and intrahepatic resistance might be appropriate to prevent the development of varices and first bleeding as mentioned previously.

Conclusion

Although variceal bleeding is not the main complication of liver cirrhosis, it remains a dramatic and life-threatening event for the patient. Propranolol, ligation, and carvedilol are good options to prevent first bleeding. Their prophylactic use should be tailored according to the individual situation of the patient (Fig. 7.3). The best pre-primary prophylaxis is interruption of the underlying disease.

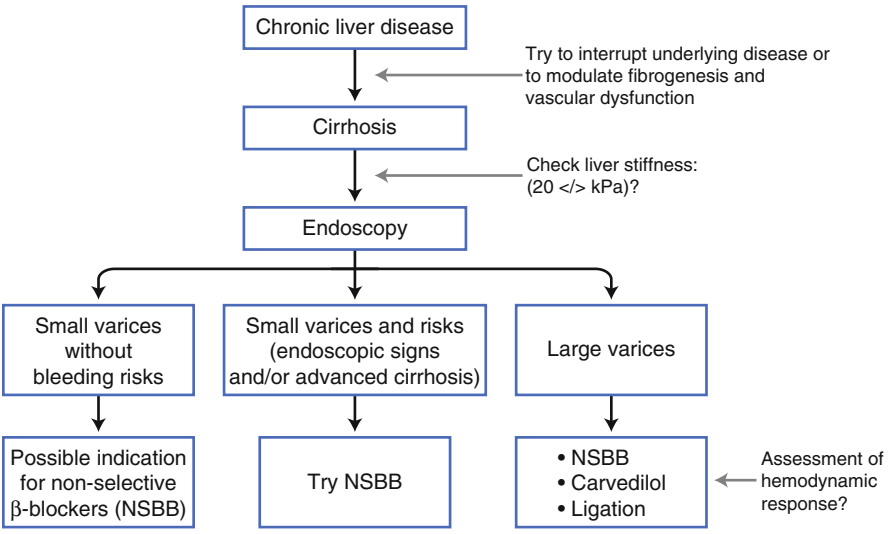

Fig. 7.3 An algorithm for prevention of variceal bleeding in patients with chronic liver disease. (Dosages: 40–160 mg/day propranolol, 6.25–25 mg carvedilol/day; Ligation: till obliteration (usually 2–3 sessions with 2–3 weeks interval)

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Chapter 8
HVPG-Guided Prophylaxis

Alessandra Dell'Era and Francesca Iannuzzi

Abbreviations

HVPG	Hepatic vein pressure gradient
FHVP	Free hepatic vein pressure
WHVP	Wedged hepatic vein pressure
TIPS	Transjugular intrahepatic portosystemic shunt

Introduction

Portal hypertension is defined as an increase of the pressure in the portal vein system.

Before 1951, when the gradient of pressure between the portal vein and the inferior vena cava (hepatic vein pressure gradient or HVPG) was introduced as a technique to estimate the degree of portal hypertension [1], portal pressure was assessed by invasive techniques, such as splenic pulp manometry, percutaneous transhepatic, or transvenous catheterization of the portal vein. Nowadays portal hypertension is generally assessed using HVPG measurement.

Portal hypertension is defined by values of HVPG above the normal range of 1–5 mmHg. When the HVPG rises to values ≥10 mmHg, the threshold for clinically significant portal hypertension [2], complications of portal hypertension

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can arise, such as esophageal varices, esophageal variceal bleeding, ascites, hepatic encephalopathy, characterizing, in the setting of portal hypertension due to cirrhosis of the liver, the transition from a compensated to a decompensated state of cirrhosis [3–6].

Measurement of HVPG

The procedure is performed under local anesthesia mainly via the internal jugular or femoral vein using a balloon catheter. HVPG is, then, obtained by catheterization of a hepatic vein and measurement of the difference between the wedged hepatic venous pressure (WHVP), obtained by occluding the vein, and the free hepatic venous pressure (FHVP), with the catheter not occluding the hepatic vein. The occlusion of one hepatic vein stops blood flow in the hepatic veins and in the sinusoids equalizing the pressure in the occluded position to the pressure in the sinusoids. In the normal liver the WHVP is slightly lower than portal pressure but in liver cirrhosis with viral or alcoholic etiology the WHVP gives an accurate estimate of portal pressure [7, 8]. In case of cirrhosis HVPG equals portal pressure while in case of pre-sinusoidal portal hypertension (e.g., schistosomiasis, idiopathic portal hypertension) or in prehepatic portal hypertension (e.g., portal vein thrombosis) HVPG is normal or slightly increased [7–10].

Several guidelines have been published on how to measure HVPG [11, 12] because, if measured inaccurately, it is not useful and can complicate the management of the patient. The required equipment to properly measure HVPG is composed by a recorder capable of producing a permanent tracing of pressure values (with an upper limit of about 30–40 mmHg) with a quartz pressure transducer that can detect changes in venous pressure and an occlusion balloon catheter. When measuring the WHVP or the FHVP operators should wait for the stabilization of the venous pressure and all measures should be repeated at least three times to check the reproducibility. In order to avoid an underestimation of the WHVP one must check (by injecting 5 ml of contrast medium through the tip of the catheter) that the inflated balloon completely occludes the hepatic vein and that no venous-to-venous shunts are present distally to the inflated balloon. All pressure tracings should be recorded and printed so that they can be reviewed by independent observers.

HVPG must be measured as the difference of wedged and free hepatic venous pressures because, in this way, it is not influenced by changes in intra-abdominal pressure (e.g., for ascites) and by inadequate positioning of the external zero reference point. The hepatic-atrial pressure gradient, suggested by some authors to better reflect the variceal hemodynamics, should not be used because, as shown by a work of La Mura et al. [13] it does not correlate with HVPG and does not provide the excellent prognostic information HVPG gives when used to evaluate the response to drug treatment.

The measurement of the WHVP should be done by inflating the balloon on the tip of a balloon catheter in a large hepatic vein, as firstly described by Groszmann

et al. [14], and not by wedging the catheter in a small venule to block the blood flow [9, 15] because it allows to evaluate HVPG over a larger volume of the liver in a more reproducible way [5, 16–19].

HVPG measurement is a safe procedure with 0–1 % minor complications in large series of patients [20, 21].

HVPG in the Evaluation of Response to Medical Treatment of Portal Hypertension

Primary and Secondary Prophylaxis

HVPG measurement in clinical practice has been assessed in different contexts. It has been shown that esophageal varices do not develop unless HVPG rises ≥10 mmHg [3, 5] and that variceal bleeding does not occur until the threshold of 12 mmHg has been reached [5]. In a study by Vorobioff et al., it was shown that the reduction of HVPG ≤12 mmHg, because of an improvement in liver function, leads to a complete prevention of variceal bleeding [22].

The role of HVPG monitoring on the risk of variceal bleeding in primary and secondary prophylaxis has been evaluated. In fact, as described in specific chapters, chronic pharmacological therapy may be used to decrease pressure in the portal system.

Several studies have shown that the decrease of HVPG to ≤12 mmHg by chronic treatment, in primary and secondary prophylaxis [6, 22–24] completely prevents variceal bleeding. In case of a reduction ≥20 % from baseline, even though not below 12 mmHg, there is still a protection from variceal bleeding [23].

About 30–40 % of patients in primary prophylaxis and 40–50 % in secondary prophylaxis achieve a reduction in HVPG ≤12 mmHg or ≥20 % during chronic medical treatment for portal hypertension and can be considered good hemodynamic responders [23, 25–29]. Those patients who do not achieve an hemodynamic response are considered nonresponders and their risk of bleeding is about 30–40 % at 2–3 years in primary prophylaxis [6, 27, 30] and 46–65 % in secondary prophylaxis [31].

The evaluation of the response to pharmacological treatment means measuring HVPG values at least twice, the first time before starting drug therapy and the other during chronic treatment; a third measurement may be needed in case we add other drugs (i.e., ISMN) to beta-blockers in secondary prophylaxis [32, 33]. Although minimally, HVPG measurement is an invasive procedure and may produce discomfort to patients. La Mura et al. [34] retrospectively evaluated 166 cirrhotic patients who received acute i.v. propranolol during hemodynamic study (0.15 mg/kg) and were subsequently treated with chronic beta-blocker therapy in primary and secondary prophylaxis. They showed that being a good responder in the acute study was associated to a reduction in bleeding and rebleeding rates at 2 years (responders vs. nonresponders: 12 % vs. 23 % in primary prophylaxis and 23 % vs. 46 % in

secondary prophylaxis). Villanueva et al. [35] assessed in a prospective study the long-term prognostic value of hemodynamic response to acute propranolol intravenous administration. A correlation between acute and chronic changes in HVPG was present and a reduction of HVPG >10 % from baseline was found to be the best cut-off for identifying patients at risk of bleeding. Although these data are promising, further studies are required on this issue.

One important point, still not resolved, is the timing of re-measurement of HVPG [36]. In a paper by Thalheimer et al. [37] a thorough revision of the papers using HVPG monitoring for secondary prophylaxis published so far was performed [23, 28, 38, 39]. It showed that a great heterogeneity of time interval (ranging from 1 to 5 months) between the two measurements was present and that many patients could not have a second HVPG measurement because of intercurrent bleeding: between 25 and 44 % of rebleeders rebled before re-measurement.

One of the problems of HVPG-guided pharmacological therapy is the choice of an alternative treatment for patients who are hemodynamic nonresponders. The studies published so far have shown that endoscopic band ligation might be a suitable option [30, 40] even if this should be demonstrated in larger studies. In fact, it is possible that patients who do not respond or are not suitable for one treatment may also be less suitable for other treatments because of comorbidity, poor compliance, and other still unknown factors.

Finally, patients are defined as hemodynamic responders according to two consecutive HVPG measurements performed only a few months apart. Weather the hemodynamic response is maintained on long term has been evaluated in only few studies [41, 42]. According to these studies, 58–81 % of patients maintain the response and are protected from bleeding and death; those who do not present also a worsening of liver function and the loss of response appears to be an independent predictor of death [42]. It remains to be clarified if the prognostic information we can obtain by serial HVPG measurement is worth the cost and the discomfort for the patient.

Acute Bleeding

Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care for patients with acute variceal bleeding [43, 44]. However, treatment failure (i.e., failure to control bleeding, early rebleeding, or death) occurs in 10–15 % of patients [45, 46]. In these patients transjugular intrahepatic portosystemic shunt (TIPS) placement may be considered as a rescue treatment [43, 47].

In a study by Moitinho et al. [48] early HVPG measurement has been evaluated in the setting of acute variceal bleeding and it was shown that an HVPG $\geq$20 mmHg was a predictor of high risk of treatment failure. This value was used as the cut-off to place an early TIPS in a study by Monescillo et al. [49], and the authors showed that the early use of TIPS in high risk patients was associated with a significant reduction in treatment failure and mortality.

Conclusion

HVPG measurement can be extremely useful as a guide for therapy in primary, secondary prophylaxis and acute treatment of variceal bleeding, and therefore its use should be encouraged in clinical practice to obtain important information on prognosis and response to pharmacological therapy [50], provided the measurement is performed properly.

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Part III
Treatment of Acute Variceal Hemorrhage

Chapter 9
Transfusion Policy

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Introduction

Hypovolemic shock is the most common form of shock. It can be a consequence of acute gastrointestinal hemorrhage. In acute bleeding hypovolemic shock results from the loss of plasma volume and red blood cell (RBC) mass, and can induce an inadequate tissue perfusion of oxygen and substrate [1]. When it is severe and/or persistent, inadequate oxygen delivery leads to irreversible cell injury. Only rapid restoration of oxygen delivery can reverse the progression of the shock state. It is essential to recognize overt and impending shock in a timely fashion and to intervene emergently to restore perfusion. This often requires the expansion of intravascular volume [2].

The physiologic response to hypovolemia includes the adaptation of cardiac output and systemic vascular resistance to maintain a level of systemic pressure adequate for the perfusion of heart and brain, at the expense of other tissues such as muscle, skin, and especially the gastrointestinal tract [2, 3]. The metabolic rates of the heart and brain are high, and their stores of energy substrate are low. These organs are critically dependent on a continuous supply of oxygen and nutrients. So, the physiologic response to hypovolemia is driven to maintain the perfusion of brain and heart by restoring an effective circulating blood volume. There is an increase in

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sympathetic activity, hyperventilation, collapse of venous capacitance vessels, release of stress hormones, and an attempt to limit the loss of intravascular volume through the recruitment of interstitial and intracellular fluid and reduction of urine output [2, 3].

Mild hypovolemia (≤20 % of the blood volume) generates mild tachycardia but relatively few external signs [4, 5]. With moderate hypovolemia (~20–40 % of the blood volume), the patient becomes increasingly anxious and tachycardic and there may be postural hypotension and tachycardia. If hypovolemia is severe (≥40 % of the blood volume), the classic signs of shock appear including marked tachycardia and hypotension, very narrow pulse pressure, and low urine output, while mental status can be markedly depressed. The transition from mild to severe hypovolemic shock can be insidious or extremely rapid [2, 3]. If severe shock is not reversed rapidly, especially in elderly patients and those with comorbid illnesses, death is imminent. A very narrow time frame separates the derangements found in severe shock that can be reversed with aggressive resuscitation from those of progressive decompensation and irreversible cell injury [6].

In resuscitation from shock, it is critical to restore tissue perfusion and optimize oxygen delivery, hemodynamics, and cardiac function rapidly [2, 3]. Initial resuscitation requires rapid reexpansion of the circulating intravascular blood volume along with interventions to control ongoing losses. Volume resuscitation is initiated with the rapid infusion of isotonic saline or a balanced salt solution such as Ringer's lactate through large-bore intravenous lines [7]. No distinct benefit from the use of colloid has been demonstrated and in trauma patients it is associated with a higher mortality, particularly in patients with traumatic brain injury [7]. The infusion of 2–3 L of salt solution over 20–30 min should restore normal hemodynamic parameters. Continued hemodynamic instability implies that shock has not been reversed and/or that there are significant ongoing blood or volume losses. In the presence of severe and/or prolonged hypovolemia, inotropic support may be required to maintain adequate ventricular performance after blood volume has been restored. Successful resuscitation also requires support of respiratory function [6]. Supplemental oxygen should be provided, and endotracheal intubation may be necessary to maintain arterial oxygenation. RBCs are used to improve oxygen delivery to tissues in case of severe anemia [8–10]. It is one of the few treatments that adequately restores tissue oxygenation when oxygen demand exceeds supply [8–10].

Mechanisms of Adaptation to Hypovolemic Anemia

Almost 20 years ago a Task Force on Blood Component Therapy of the American Society of Anesthesiologists developed evidence-based guidelines for transfusing RBCs [6]. The principal conclusions were that RBC transfusions should not be dictated by a single hemoglobin "trigger" but instead should be based on the

Table 9.1 Oxygen content, delivery, and consumption

$CaO_2 = (Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)$
$CaO_2 = Hb\ (g/dL) \times 1.34\ (mL\ O_2/g\ Hb) \times SaO_2 + PaO_2 \times 0.003\ (mL\ O_2/mmHg/dL)$
$DO_2 = \text{cardiac output} \times CaO_2$
$VO_2 = \text{cardiac output} \times (CaO_2 – CvO_2)$
$VO_2 = \text{cardiac output} \times ([Hb \times 1.34 \times (SaO_2 – SvO_2) + (PaO_2 – PvO_2) \times 0.003])$

Arterial oxygen content is a function of hemoglobin saturation, hemoglobin concentration, and the amount of oxygen physically dissolved in arterial blood and arterial oxygen transport is a function of oxygen content and cardiac output. *Hb* hemoglobin, SaO_2 arterial oxygen saturation, PaO_2 arterial partial pressure of oxygen. 1.34 corresponds to milliliters of O_2 transported by 1 g of Hb. $(0.003 \times PaO_2)$ represents dissolved O_2, not bound to Hb (in non-anemic patients breathing room air most oxygen is hemoglobin-bound and only 2 % is dissolved in the plasma)
CaO_2 arterial oxygen content, DO_2 oxygen delivery, VO_2 oxygen consumption

patient's risks of developing complications of inadequate oxygenation. RBC transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL [6, 10].

The effects of anemia must be separated from those of hypovolemia, although both can interfere with oxygen transport. Acute blood loss is managed initially by restoring volume to avoid hemorrhagic shock. In young healthy patients, losses of up to 30–40 % of blood volume usually can be treated adequately with crystalloid therapy [2, 6]. Acute loss of blood volume elicits compensatory increases in heart rate and cardiac output, as well as a rise in vasoactive hormones, redistribution of blood flow, and influx of extravascular fluid to the intravascular compartment [2–5]. Diminished oxygenation due to inadequate oxygen-carrying capacity can have serious clinical implications, primarily because of ischemic effects on the myocardium and brain. The aim of RBC transfusion is to increase arterial oxygen transport to the tissues, which depends on arterial oxygen concentration and cardiac output [6, 11]. Arterial oxygen content is a function of hemoglobin saturation, hemoglobin concentration, and the amount of oxygen physically dissolved in arterial blood (Table 9.1). In acute anemia arterial oxygen transport usually decreases as a result of decreasing hemoglobin, but it also can be due to an inefficient compensation by cardiac output (due to non-compensated volemic loss or to myocardial hypoxia and reduced ejection fraction) [6]. Oxygen transport can also decrease as a result of a decrease in SaO_2 through changes in ventilatory function and gas exchange. In healthy tissues, decreases in oxygen delivery do not lower oxygen consumption because tissue O_2 extraction increases proportionately [11]. When delivery is reduced below a critical threshold, oxygen consumption falls because tissue extraction cannot compensate for the reduction in delivery. When the body is at rest, oxygen delivery is 2–3 times greater than critical oxygen delivery threshold [11].

Reductions in arterial oxygen content in acute anemia are usually well tolerated because of compensatory increases in cardiac output. Such an increase in cardiac output is primarily due to an increase in systolic ejection volume, although heart rate increases as well [11]. In the context of hypovolemia, the capacity of cardiac output to adapt requires an adequate reposition of volemia [6]. Anemia results in reduction of blood viscosity, which favors venous return to the heart and facilitates ejection of stroke volume [3, 12]. In addition, normovolemic anemia increases sympathetic stimulation of the heart, which contributes to the increase of cardiac output [13]. The compensatory increases in cardiac output may be affected by several factors such as left ventricular dysfunction and vasoactive pharmacologic agents (such as beta-adrenergic or calcium channel blockade or hypnotics, and neuromuscular blocking drugs), necessitating a higher hemoglobin concentration for adequate oxygen delivery [12, 13]. In patients with impaired cardiac function, the increase in cardiac output is mainly due to an increase in heart rate.

Although an increase in cardiac output is the primary compensation for reduced oxygen-carrying capacity, a second global compensatory mechanism involves increasing tissue oxygen extraction which lowers venous oxygen saturation and partial pressure and includes changes in the microcirculation at the tissue level [6, 11]. Oxygen delivery decreases during progressive acute anemia despite an increase in cardiac output [3]. However, oxygen extraction also increases and thus oxygen consumption remains constant [11]. Such an increased tissue oxygen extraction is firstly due to a redistribution of blood flow from organs with a high reserve, such as skin, muscle, and the abdominal viscera, to organs with limited reserve such as the heart and brain [6, 11]. This redistribution is driven by an increase in neuroadrenergic stimulation [3]. Increased tissue oxygen extraction also leads to a recruitment of capillaries and a reduction in hemoglobin affinity for oxygen [13, 14].

When hemoglobin falls oxygen consumption remains unchanged until a critical oxygen delivery threshold is reached where compensatory cardiac output and tissue oxygen extraction can increase no further and oxygen consumption begins to drop [11]. Oxygen consumption is limited by demand above critical oxygen delivery and limited by supply below it. Patients are in serious danger of organ failure if oxygen delivery drops below this critical value. With the compensatory mechanisms, healthy normovolemic patients can tolerate hemoglobin concentrations as low as 5 g/dL without a reduction in oxygen consumption or signs of impaired oxygenation [3, 11]. This is the threshold below which oxygen consumption becomes dependent on arterial oxygen supply, and oxygen delivery is no longer sufficient to prevent tissue hypoxia. Thus, the critical threshold of oxygen delivery in individuals without comorbidity is situated at a value below hemoglobin concentration of 5 g/dL [10, 11]. At such low levels of hemoglobin subtle cognitive dysfunction may appear which reverses immediately with transfusion [15, 16]. Safety hemoglobin margin for transfusion of patients with comorbidity that may hamper compensatory mechanisms of anemia often should be higher. Case series reports of people who refuse transfusion for religious reasons indicate that some patients tolerate very low hemoglobin concentrations without an increase in mortality [17, 18]. A review of 61 reports involving 4.722 Jehovah's Witnesses identified that of 50 reported deaths,

23 were primarily due to anemia and except for 3 patients who died after cardiac surgery, all patients whose deaths were attributed to anemia died with hemoglobin concentrations ≤5 g/dL [19]. It is difficult to rely on a specific hemoglobin or hematocrit value as a "transfusion trigger," such as the outdated "10/30 rule" which stated that transfusion is necessary in patients with a hemoglobin concentration less than 10 g/dL or a hematocrit less than 30 % [20]. Furthermore defining a critical hemoglobin concentration for patients with significant medical debility whose compensatory mechanisms might be further compromised is even harder. Thus, in keeping with the classical guidelines from the American Society of Anesthesiologists regarding indications for transfusing RBCs [6], it can be stated that transfusions should not be dictated by a single hemoglobin "trigger" but instead should be based on the patient's risks of developing complications of inadequate oxygenation.

Effects of Volume Restitution on Portal Hypertension

Concerns about volume restitution and transfusion have been raised primarily with respect to patients who have cirrhosis with portal hypertension [21]. Marked abnormalities in blood volume regulation can occur during the course of cirrhosis [22, 23]. Total blood volume is increased in patients with portal hypertension, while the occurrences of acute bleeding episodes are frequent causes of hypovolemia in these cases [21, 24]. Changes in blood volume determine profound changes in portal pressure [25]. Blood volume depletion results in a fall in portal pressure, while it increases with blood volume expansion [26–28].

Blood volume depletion decreases portal venous inflow, and thereby the portal pressure, by reducing the venous return and thereby the cardiac index, but also by causing reflex splanchnic vasoconstriction in response to the fall in arterial blood pressure through the activation of endogenous neurohumoral vasoactive systems [29, 30]. In patients with portal hypertension, restitution of plasma volume can induce rebound increases in portal pressure that may precipitate portal hypertensive-related bleeding [29, 30]. Experiments in animal models of portal hypertension have shown that blood volume restitution following an hemorrhagic episode, even if not causing an expansion of the blood volume above the pre-hemorrhage values, produces an increase of portal pressure beyond baseline values, which is not observed in normal rats, and which can have detrimental effects by inducing further bleeding [29, 30]. In these experiments in portal hypertensive rat models, the fall of about 30 % in portal venous pressure during hemorrhage occurred as expected, but after blood volume restitution portal pressure rose significantly to values about 20 % higher than the baseline values [29]. This "overshoot" occurred despite unchanged splanchnic blood inflow, due to increased resistance in the portocollateral vessels mediated by the release of vasoactive mediators such as catecholamines, angiotensin, and vasopressin, during the period of hypovolemia [29]. Blood volume expansion after bleeding, by increasing portal blood flow within a territory with a raised vascular resistance, can elevate portal pressure beyond baseline values which can in

turn precipitate further bleeding [21, 31]. This rebound increase in portal pressure is not observed in normal animals, in which the portal pressure returned to baseline values with volume restitution [29]. Blood volume restitution after hemorrhage particularly worsens portal hypertension in cirrhotic rats with extensive portal-systemic shunting [30].

Experimental studies in cirrhotic rats have also investigated the influence of different strategies of blood volume restitution in the outcome of portal hypertensive bleeding [27, 31]. In these experiments, after inducing a gastrointestinal bleeding the subsequent hypovolemic shock was treated with no transfusion, with moderate transfusion (half of expected blood loss), or with total transfusion (the complete expected blood loss) [31]. Groups given no transfusion or moderate transfusion remained hemodynamically stable after transfusion. However, the group receiving the complete blood transfusion had the worse evolution [31]. Thus, the group receiving total transfusion continued to deteriorate with persistent bleeding, greater blood loss, and progressive fall in arterial pressure and had the worst survival (all animals died). On the other hand, the group with moderate transfusion had better survival than the group without transfusion at all [31]. These results strongly support the concept that blood volume restitution during a hemorrhage may be detrimental, unless it is done very conservatively [21, 32].

Clinical studies have also shown that blood transfusion during the course of an acute variceal bleeding episode [33, 34] significantly increases portal pressure in patients with cirrhosis and portal hypertension, an increase that may be prevented with somatostatin [33]. It has been shown that somatostatin, probably by preventing the release of vasoactive peptides, can also prevent further secondary rises in portal pressure during acute hemorrhage, such as those induced by transfusion, whereas such a stabilization of portal pressure may reduce the risk of further hemorrhage [33]. A recent RCT on transfusion strategies for upper gastrointestinal bleeding, in which randomization was stratified according to the presence or absence of liver cirrhosis, has shown beneficial effect of restrictive transfusion strategy with respect to further bleeding which was observed mainly in patients with portal hypertension [35]. This study showed that despite treatment with somatostatin, patients in the liberal-strategy group had a significant increase in portal pressure during acute variceal bleeding that was not observed in patients in the restrictive-strategy group. This may have accounted for the higher rate of further bleeding with the liberal transfusion strategy.

Potentially Harmful Effects of Transfusion on Hemostatic Mechanisms

It has been speculated that the early clot formed around a bleeding vessel is fragile and capable of dislodgement if the compensatory hypotension induced by hemorrhage is abolished by repletion of blood volume, and that transfusion may also

Table 9.2 Potential inconvenients of transfusion in gastrointestinal bleeding

Risk of further bleeding
• Clot blow-out: early clot is fragile and capable of dislodgement if compensatory reduction of vessel pressure/flow is not allowed (*increased pressure/flow may dislodge clots* and *impair formation of new clots*)
• Change in coagulation properties
– Disturbing platelet aggregation
– Diluting clotting factors
– Altering coagulation cascade
• Transfusion in cirrhosis may lead to a rebound increase of portal hypertension (increased risk of further bleeding)
Risk of complications
• Changes in stored red cells (storage lesion)
• The duration of RBC storage before transfusion may alter RBC function and, therefore, influence the incidence of complications
• Possibility of immunosuppressive effect

Potential inconvenients (some of them hypothetical) have been related to transfusion of RBC. These potential effects can increase the risk of further bleeding, complications, and even death

impair the coagulation properties [32, 36]. The treatment of hemorrhagic shock should maintain blood pressure and tissue perfusion until bleeding is controlled [36]. However, different studies support the concept that, in hypovolemic shock, the depression of the blood pressure may allow the rapid control of hemorrhage while an excessive restitution in blood pressure, before effective hemostasis can be achieved, may be followed by fresh bleeding [36, 37]. Thus, although maintenance of blood pressure might prevent shock, it could worsen bleeding [37]. For years, some experimental and clinical studies have raised concerns on whether an excessive elevation in blood pressure during the recovery of hypovolemic shock may precipitate further bleeding (Table 9.2) [32, 36, 37]. Raising of blood pressure can increase tissue perfusion and tissue oxygenation, but the increased pressure might impair the formation of new blood clots or dislodge existing ones [36, 37]. Some reports suggest that efforts to return blood pressure to normal in bleeding trauma patients can be counterproductive [36]. Although vigorous fluid resuscitation might be lifesaving in some patients, results from clinical trials are consistent with results from animals with uncontrolled hemorrhage which show that raising of blood pressure could worsen bleeding and increase mortality [36, 37]. These harmful effects of transfusion may also be related to an impairment of hemostasis [38–41]. Transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia, inducing an increase in splanchnic blood flow and pressure that may impair the formation of clots. Fluid resuscitation may affect the process of hemostasis at different stages, such as altering platelet aggregation or diluting or reducing clotting factors [32, 36, 37]. Transfusion may also induce abnormalities in coagulation properties [8, 10]. Furthermore, some studies suggested that a conservative approach to recover volemia in hypovolemic shock was associated with lower rebleeding rates and lower recourse to urgent surgery.

Risks of Transfusion

Transfusions are not without risks or costs [42, 43]. The transmission of infectious diseases such as hepatitis B or C or human immunodeficiency virus infection, hemolytic and nonhemolytic transfusion reactions, immunosuppression, alloimmunization, and other complications are all well known potential sequels of blood component therapy. Screening for transfusion-associated infections has largely improved and has dramatically reduced their incidence [44]. However, noninfectious complications of transfusion still cause morbidity, and even mortality, associated with transfusion (Table 9.3).

Nonhemolytic transfusion reactions, often manifested by fever, chills, or urticaria, are the most common adverse effects of RBC transfusion [42, 45]. Other less common complications associated with transfusion lead to greater related morbidity and even mortality, such as transfusion-related acute lung injury (TRALI) or transfusion-associated circulatory overload (TACO) [42, 45–47]. Other potential risks associated with transfusion raise concerns at present such as the effects of transfusion on the immune system or transfusion-related immunomodulation

Table 9.3 Potential complications of blood transfusion

Immune-mediated reactions
Febrile reaction
Urticaria or other cutaneous reaction
RBC alloimmunization
Mistransfusion
Hemolytic reaction
Fatal hemolysis
TRALI
TRIM
Anaphylaxis
GvHD
Nonimmune reactions
TACO
Hypotensive reactions
Transfusion-related iron overload
Microchimerism
Posttransfusion purpura
Coagulopathy
Other: hypocalcemia, hypokalemia, hypothermia

TRALI transfusion-associated acute lung injury, *TRIM* transfusion-related immunomodulation, *GvHD* graft vs. host disease, *TACO* transfusion-associated circulatory overload

(TRIM) [48, 49], and the storage lesion which consists of biochemical and molecular changes and an accumulation of inflammatory mediators that develop over time in stored red cells [50]. Long storage times may influence the quality of blood that is transfused. During storage, red cells undergo a number of physical and chemical changes, including increased rigidity of the membrane, loss of organic phosphates, and the generation and release of proinflammatory cytokines [51, 52]. Such changes may contribute to the poorer clinical outcomes that have been associated with the transfusion of old blood [52]. Observational studies suggest that the storage lesion could be responsible for transfusion-associated complications such as immunosuppression and multiple organ failure syndrome and has been associated with higher risk of mortality [52, 53].

Transfusion Strategy in Gastrointestinal Bleeding

Acute upper gastrointestinal bleeding is a common emergency associated with non-negligible rates of morbidity and mortality [54]. It is one of the most common indications for RBC transfusion [55] because acute blood loss can decrease tissue perfusion and tissue oxygen delivery [56]. RBC transfusion may be lifesaving in patients with massive exsanguinating bleeding. However, in most cases hemorrhage is not so severe and transfusion is aimed to address anemia rather than to fluid resuscitation [57]. In such circumstances, the optimal timing and intensity of RBC transfusion are controversial [58–61]. Overall, RBC transfusion requirements have been increasing in western nations in recent decades [62]. However, as previously commented, transfusions are not without risks or costs. Because of this, in recent years, there has been increased research to optimize the benefits associated with RBC transfusion [63, 64]. Different studies have demonstrated that restricted transfusion strategies may be appropriate in some settings. Observational studies performed in critically ill patient settings have shown higher mortality in patients who received transfusion than in those who did not [65]. RCTs have also shown that a restrictive transfusion strategy did not worsen [66, 67] and even improved [68] the mortality observed with liberal transfusion strategy. The Transfusion Requirements in Critical Care (TRICC) study was a pioneer prospective, adequately powered, randomized trial, which investigated the impact of blood transfusion on outcome in acutely ill adult patients [68]. The TRICC study compared a “liberal (10 g/dL)” vs. “restricted (7 g/dL)” transfusion trigger threshold in 838 ICU patients. In this study, the restrictive transfusion threshold in addition to significantly reducing blood use was at least equivalent, and in some patients (adults <55 years of age or Acute Physiology and Chronic Health Evaluation score <20) achieved better survival than the more liberal transfusion threshold. A subsequent study in pediatric patients reported similar results. However, these studies excluded patients with gastrointestinal bleeding [66]. Observational studies and small RCTs have suggested that RBC transfusion may be harmful in patients with hypovolemic anemia [69, 70], even in patients with acute upper gastrointestinal bleeding [71–73].

Current international guidelines recommend decreasing the hemoglobin threshold level for transfusion from around 10 g/dL [58, 61] to around 7 g/dL [60, 74]. A reduction in the number of transfusions performed may have accounted for the improvement in mortality from gastrointestinal bleeding observed in recent years [75, 76]. However, current guidelines are based on controlled trials on transfusion triggers performed in critically ill patients with normovolemic anemia, from which patients with acute gastrointestinal bleeding have usually been excluded [77]. Transfusion requirements in patients with acute gastrointestinal hemorrhage may be different due to factors such as hemodynamic instability or rapid instauration of anemia to low hemoglobin levels [54–57]. Observational studies and RCTs of RBC transfusion in critically ill patients have shown little evidence of benefit, but some evidence of harm [65–68]. In acute gastrointestinal bleeding, both a previous small study [71] and a recent observational study [73] have suggested an increased risk of rebleeding with blood transfusion. Restrictive transfusion was also supported by another small study [72]. These harmful effects of transfusion may be related to an impairment of hemostasis [71]. Transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia inducing an increase in splanchnic blood flow and pressure that may impair the formation of clots [32, 36]. Furthermore, transfusion may also induce abnormalities in coagulation properties [39–41].

A recent randomized, controlled trial performed in our unit assessed whether a restrictive threshold for red cell transfusion in acute gastrointestinal bleeding is more effective and safer than a liberal transfusion strategy that was based on the threshold recommended in guidelines at the time the study was designed [58, 61]. Patients with massive exsanguinating hemorrhage were excluded from the trial because current knowledge indicates that red-cell transfusion may be lifesaving in these critically ill bleeding patients [35]. However, only a minority of eligible patients (3 % of cases) presented with such a massive bleeding during the period of the study. Patients with low rebleeding risk, as derived from favorable clinical parameters (clinical Rockall score of 0 plus hemoglobin at admission >12 g/dL), were not included in this study and, in fact, this was the main reason for exclusion [35]. However, these patients would rarely require transfusion. Furthermore, patients with recently symptomatic cardiovascular diseases, among others, were also excluded from our study because the transfusion threshold may be different in these patients. Nine hundred and twenty one patients with severe acute upper gastrointestinal bleeding were enrolled in this study and randomly assigned, 461 of them to a restrictive-strategy group, with a hemoglobin threshold for transfusion of 7 g/dL and a target range after transfusion of 7–9 g/dL, and 460 to a liberal-strategy group, with a hemoglobin threshold for transfusion of 9 g/dL and a target range after transfusion of 9–11 g/dL, which was standard care at the time of trial design [58, 61]. Randomization was stratified according to the presence or absence of liver cirrhosis. A total of 225 patients assigned to the restrictive-strategy patients (51 %) and 65 assigned to the liberal-strategy patients (14 %) did not receive transfusions ($P<0.001$) [35]. The lowest hemoglobin concentration within the first 24 h was significantly lower in the restrictive-strategy group. The daily lowest hemoglobin concentration was significantly lower in the restrictive-strategy group each day up

to discharge ($P<0.001$), but hemoglobin concentration at 45 days was similar in the two groups. The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95 % vs. 90 %; HR = 0.55, 95 % CI = 0.33–0.92; $P=0.02$). Further bleeding occurred in 10 % vs. 16 % of patients, respectively ($P=0.01$), and adverse effects in 40 % vs. 48 % ($P=0.02$). Survival probability was slightly higher with restrictive transfusion strategy than with liberal strategy in the subgroup bleeding from peptic ulcer (HR = 0.70, 95 % CI = 0.26–1.25). Survival probability was significantly higher with restrictive transfusion strategy in the subgroup of patients with cirrhosis and Child-Pugh class A or B (HR = 0.30, 95 % CI = 0.11–0.85) but not in those with Child-Pugh class C (HR = 1.04, 95 % CI = 0.45–2.37). In patients with variceal bleeding, a baseline hemodynamic study was performed within the first 48 h in 86 patients in the restrictive-strategy group and in 89 patients in the liberal-strategy group and was repeated 2–4 days later to assess changes in 74 and 77 patients, respectively. As compared with the baseline study, patients in the liberal-strategy group had a significant increase of HVPG in the second hemodynamic study (from 20.5 ± 3 to 21.4 ± 4 mmHg, $P=0.003$). There were no significant differences between the two hemodynamic studies in the restrictive-strategy group.

Recommendations on RBC Transfusion

A single hemoglobin "trigger" may help to decide transfusion. However, the final decisions regarding transfusion should be based on clinical judgment of patient's risks in each case. Blood transfusion should be based on the risk of patient for complications from inadequate oxygenation rather than by a fixed hemoglobin level. The threshold for transfusion for each patient should be based on his or her underlying condition, hemodynamic status, and markers of tissue hypoxia in acute situations. Some years ago, the American Society of Anesthesiologists concluded that RBC transfusion is rarely indicated when hemoglobin level is greater than 10 g/dL and is almost always indicated when the level is less than 6 g/dL [6].

Available evidence favors initiating RBC transfusions for most patients with acute gastrointestinal bleeding when hemoglobin levels decrease to less than 7 g/dL, with a target level of 7–9 g/dL, in the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage [35]. In keeping with it, this is the currently recommended international guideline [60, 74]. However, the threshold for transfusion may be higher in patients with massive hemorrhage or in those with underlying conditions that preclude an adequate physiological response to acute anemia.

The goal of resuscitation from hypovolemic shock is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability. RBCs are used to improve oxygen delivery to tissues in case of severe anemia, but only rarely as part of fluid resuscitation in actively bleeding patients. Ongoing blood volume losses should be controlled as soon as possible. Blood volume resuscitation should be undertaken promptly but with caution because a vigorous

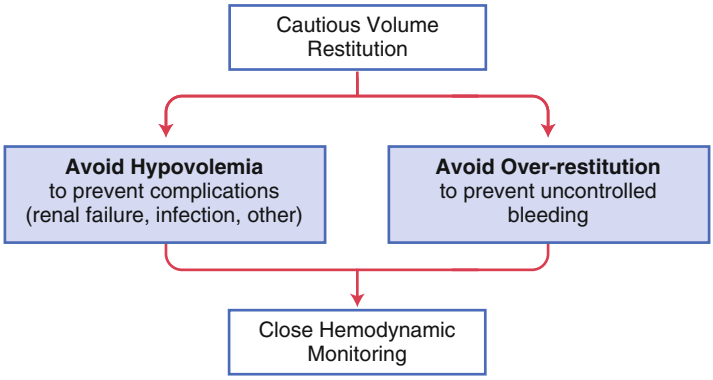

Fig. 9.1 Restitution of volemia in gastrointestinal bleeding. Blood volume resuscitation should be undertaken promptly but with caution because although volume restitution is, obviously, basic to prevent the complications related with hypovolemia, a vigorous restitution may increase the risk of further bleeding

restitution may increase the risk of further bleeding (Fig. 9.1). Such risk can be particularly high in bleeding related to portal hypertension, a condition in which an excessive volume restitution can lead to rebound increases in portal pressure, increasing risk of further bleeding and mortality.

Transfusion of Fresh Frozen Plasma and Platelets

Transfusion of fresh frozen plasma and platelets can be considered in patients with acute gastrointestinal bleeding and significant coagulopathy and/or thrombocytopenia. Scarce information is available to define precisely when transfusion of a blood component, such as platelets or plasma, should be given for gastrointestinal bleeding, particularly in patients with cirrhosis [9, 78–80].

A platelet count should be obtained, whenever possible, before transfusion of platelets. In bleeding patients, platelet transfusion is rarely indicated if the platelet count is known to be greater than 100×10^9/L and can be considered when the count is below 50×10^9/L [9, 79]. In cirrhotic patients with acute gastrointestinal bleeding platelet transfusion should be particularly considered with a platelet count below $30–40 \times 10^9$/L [9].

PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis [78]. This is because the test measures the amount of thrombin generated in plasma only as a function of the procoagulant drivers. However, in patients with cirrhosis a parallel decrease of both procoagulants and anticoagulants is now recognized, and evidence has been gained showing that prothrombin-time test and related tests are not adequate to assess the risk of hemorrhage in such patients [78]. It is now recognized that, in cirrhosis, INR reflects liver dysfunction but not bleeding

risk. In fact, the use of recombinant activated factor VII (rFVIIa), which can correct prothrombin time in cirrhotics, has been evaluated in multicenter placebo-controlled trials in cirrhotic patients with gastrointestinal hemorrhage. Such trials failed to show a beneficial effect with the addition of rFVIIa to standard therapy [81, 82].

Patients who require massive-transfusion present dilutional complications resulting from large volumes of RBC transfused. Although at present there is no accurate guide, transfusion of plasma and platelets will be required [83].

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Chapter 10
Antibiotic Prophylaxis in Acute Variceal Hemorrhage

Javier Fernández

Abbreviations

ACLF	Acute-on-chronic liver failure
GALT	Gut-associated lymphoid tissue
IV	Intravenous
SBP	Spontaneous bacterial peritonitis

Introduction

Patients with cirrhosis have increased risk to develop bacterial infections. Clinical risk factors are upper gastrointestinal hemorrhage, poor liver function, low protein ascites, prior spontaneous bacterial peritonitis (SBP), and hospitalization [1, 2]. Infection is present at admission or develops during hospitalization in about 25–35 % of patients with decompensated cirrhosis, a figure that increases up to 66 % in patients with gastrointestinal hemorrhage in the absence of antibiotic prophylaxis [1–4]. SBP and urinary tract infections are the most frequent infections followed by spontaneous and secondary bacteremia, pneumonia, and skin/soft tissue infections.

Bacterial infection has an important clinical impact on the outcome of patients with advanced cirrhosis. Cirrhotic patients present an increased risk to develop sepsis, severe sepsis, and death [1, 2, 5, 6]. Infection may also precipitate variceal hemorrhage by increasing portal pressure and altering hemostasis [7–11]. It plays also a major role in the pathogenesis of other types of decompensation of cirrhosis

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such as hepatic encephalopathy [12] and acute-on-chronic liver failure (ACLF) [13]. Antibiotic prophylaxis is therefore an essential point in the management of patients with cirrhosis and variceal hemorrhage [14–17]. The current chapter describes the pathogenesis, incidence, and clinical impact of bacterial infections in patients with cirrhosis and upper gastrointestinal bleeding and summarizes the prophylactic strategies currently recommended in this population.

Pathogenesis of Bacterial Infections in Variceal Hemorrhage

Bacterial infection is a major problem in patients with cirrhosis and upper gastrointestinal hemorrhage. Several factors contribute to increase the susceptibility of cirrhotic patients with gastrointestinal bleeding to develop infections (Fig. 10.1). Pioneer studies showed that enhanced intestinal bacterial translocation [18]—the main mechanism involved in the pathogenesis of spontaneous infections in patients with cirrhosis [19]—and reticuloendothelial system activity depression related to hypovolemia play an important role in cirrhotic patients with gastrointestinal bleeding [20, 21].

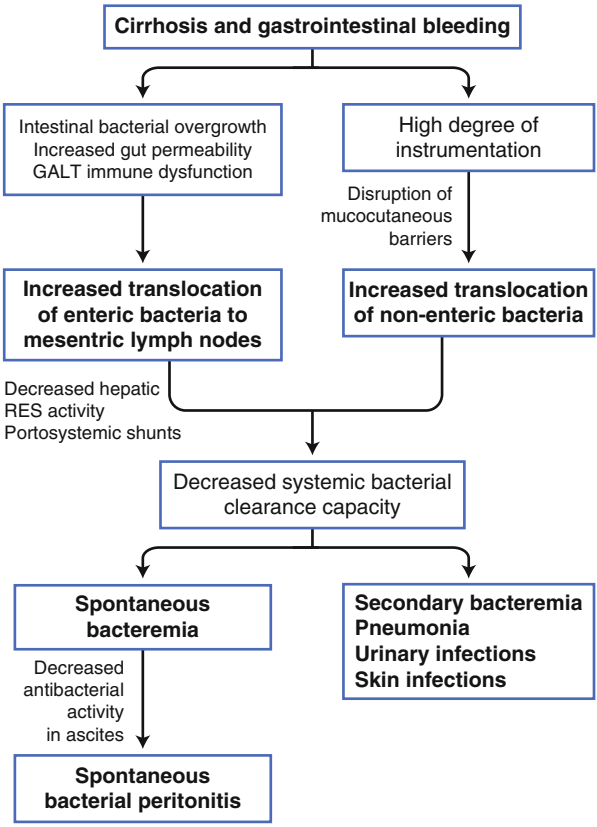

Fig. 10.1 Intestinal bacterial overgrowth, intestinal mucosal barrier dysfunction, gut-associated lymphoid tissue (GALT) immune dysfunction, and high degree of instrumentation of patient contribute to translocation of enteric and non-enteric bacteria from the intestinal lumen and extra-intestinal sites (respiratory tract, skin) to the systemic circulation in cirrhotic patients with upper gastrointestinal bleeding. Decreased systemic and peritoneal antibacterial capacity facilitates the development of bacteremia (either spontaneous or secondary), urinary and respiratory infections, and spontaneous bacterial peritonitis

Further investigations have also demonstrated that intestinal mucosal barrier plays a role in the pathogenesis of bacterial translocation and infection in cirrhosis. Intestinal mucosal barrier function deteriorates during the bleeding episode leading to impaired gut permeability and to increased bacterial translocation. A recent study has shown that increased intestinal permeability, defined by a high intestinal permeability index, is an independent predictor for proven or possible bacterial infections in patients with advanced cirrhosis and gastrointestinal bleeding. Hemorrhagic shock, ischemia–reperfusion, and oxidative damage aggravate gut barrier dysfunction and secondarily increase intestinal permeability [22, 23]. Small intestinal bacterial overgrowth could also be accentuated by decreased intestinal motility related to high adrenergic tone during the bleeding episode thus contributing to accentuate bacterial translocation [19]. It is also well known that innate and adaptive immune responses are impaired in cirrhosis leading to reduced phagocytic and killing capacity of bacteria. The poorer the liver function, the higher the impairment of immune function. Deficiencies in intestinal (gut-associated lymphoid tissue: GALT) and systemic immune host defense against invading bacteria are accentuated in patients with severe hemorrhage, especially in those developing shock [2, 21, 24]. Finally, patients with upper gastrointestinal bleeding usually require multiple invasive manipulations, central line insertion, and urinary catheterization among others, a feature that increases the risk to develop secondary infections caused by nonclassical pathogens or multidrug-resistant bacteria [3, 25].

The incidence of infection is particularly high in patients with advanced liver failure and/or severe hemorrhage [26–28]. This feature is probably related to the fact that pathogenic alterations (immune dysfunction, gut permeability, intestinal hypomotility, and invasive manipulation) are accentuated in these patients, thus leading to a higher rate of bacterial translocation and bacterial infection.

It is important to underline that very few studies have evaluated the intrinsic mechanisms leading to the development of bacterial infections in patients with cirrhosis and gastrointestinal bleeding. Experimental studies are also scarce. Some of the pathogenic theories described in this section are extrapolations coming from patients or experimental models of cirrhosis and ascites. Further investigations focused on the specific mechanisms involved in the pathogenesis of bacterial translocation and infection in patients with cirrhosis and variceal bleeding are needed.

Incidence, Timing, Risk Factors, and Type of Bacterial Infections

Bacterial infections are much more common in cirrhotic patients with upper gastrointestinal bleeding than in those admitted to the hospital due to other types of clinical decompensation. The incidence of infection in bleeding patients ranges between 16 (compensated cirrhosis) and 66 % (advanced cirrhosis) in the absence of antibiotic prophylaxis with a mean incidence of 36 % (Table 10.1) [9, 26, 28–39]. This infection rate is significantly higher than that reported in the general population

Table 10.1 Incidence of bacterial infection in patients with cirrhosis and gastrointestinal bleeding. Impact of antibiotic prophylaxis

Study	Number of patients	Intervention	Incidence of bacterial infection (%)
Trials comparing antibiotics with no intervention/placebo			
Rimola et al. [29]	140	No antibiotic prophylaxis	35
		Oral nonabsorbable antibiotics[a]	16
Soriano et al. [30]	119	No antibiotic prophylaxis	37
		Oral norfloxacin	10
Rolando et al. [31]	100	IV saline solution	23
		IV imipenem before and after sclerotherapy	21
Blaise et al. [32]	91	No antibiotic prophylaxis	66
		IV/oral ofloxacin, amoxicillin-clavulanic acid before endoscopy	20
Pauwels et al. [28]	55 Child-Pugh A-B patients and no rebleeding	No antibiotic prophylaxis	18
Pauwels et al. [28]	64 Child-Pugh C patients or rebleeding	No antibiotic prophylaxis	53
		IV/oral ciprofloxacin and amoxicillin-clavulanic acid	13
Hsieh et al. [33]	120	No antibiotic prophylaxis (placebo)	45
		Oral ciprofloxacin	10
Hong et al. [34]	40 Child-Pugh B-C patients	No antibiotic prophylaxis	45
		IV ciprofloxacin	10
Lin et al. [35]	97	No antibiotic prophylaxis	26
		IV cefazolin/oral cephalexin	6
Hou et al. [9]	120	No antibiotic prophylaxis	26
		IV/oral ofloxacin	3
Xu et al. [36][d]	113	No antibiotic prophylaxis	38
		IV cefazoline	16
Trials comparing different antibiotics			
Sabat et al. [37]	56 High risk patients[b]	Oral norfloxacin	18
		Oral norfloxacin + IV ceftriaxone	12.5
Fernández et al. [26]	111 High risk patients[c]	Oral norfloxacin	33
		IV ceftriaxone	11
Diaz Ferrer et al. [38]	98	IV ciprofloxacin	18
		IV cefazolin	11
Wu et al. [39][d]	102	IV cefazolin	14
		IV ceftriaxone	10

[a]Gentamicin + vancomycin + nystatin or neomycin + colistin + nystatin
[b]Ascites, hepatic encephalopathy, or shock
[c]At least two of the following: ascites, hepatic encephalopathy, jaundice, severe malnutrition
[d]Retrospective study

of cirrhotic patients admitted to the hospital due to clinical decompensation (25 %) [4]. Risk for bacterial infection is mainly observed in the first 5–7 days after hemorrhage [1, 28–30, 40]. Infections show a bimodal distribution but tend to occur early during hospitalization: about two thirds are present at hospital admission (community-acquired infections) while the remaining one third develop during hospitalization. Bacteremia (19–56 %), SBP (19–37 %), urinary infections (12–34 %), and pneumonia (12–19 %) are the most frequent infections [26–30].

Risk of infection is not the same for all cirrhotics with gastrointestinal bleeding. Clinical risk factors are poor liver function (Child-Pugh class C, ascites, jaundice, or hepatic encephalopathy), malnutrition, severity of the initial hemorrhage, and failure to control bleeding or rebleeding [1, 26–28]. The degree of hepatic insufficiency is without any doubt the main factor determining the risk for infection in this setting. Incidence of bacterial infections in patients with preserved liver function (Child-Pugh class A) is around 10–15 %, 20–35 % in Child-Pugh B patients, and 50–60 % in Child-Pugh C patients [28, 41]. Hepatic encephalopathy and ascites have also been identified as independent predictive factors for bacterial infection in bleeding cirrhotic patients [27]. Factors related to the severity of the bleeding episode have also a clear impact on the risk of infection [9, 26–28]. Several studies have shown that hypovolemic shock, high transfusion requirements (more than 2 blood units), failure to control bleeding, and rebleeding increase significantly the risk of developing infection. Instrumentation, higher in patients with severe bleeding, is also a factor that favors the development of nosocomial bacterial infections in these patients [3, 25].

Clinical Significance of Infection

The first studies evaluating the prognostic significance of bacterial infection in bleeding cirrhotic patients showed that infection is associated with poor outcome [7, 9, 28, 41]. These studies showed that infection is independently associated to failure to control bleeding and increases the risk of early rebleeding. In the study by Goulis et al., 79 % of patients with and 36 % of those without failure to control bleeding were infected [7]. Hou et al. demonstrated that antibiotic prophylaxis can prevent not only infection but also early rebleeding as well as decrease the amount of blood transfused in patients with acute variceal bleeding. Seventy-two percent of the infected patients and 26 % of non-infected patients had rebleeding. Bacterial infection increased almost fourfold the risk of rebleeding [9]. Timely administration of prophylactic antibiotics is also associated with reduced rebleeding rate [42]. Two pathogenic alterations induced by infection can explain these findings: first, endotoxemia and infection derange systemic and splanchnic hemodynamics in cirrhosis thus increasing portal pressure; second, infection impairs hemostasis and worsens liver function [7–11]. Therefore, infection may precipitate variceal bleeding [8, 10, 11], is a causative factor in early variceal rebleeding [9], may induce hepatorenal syndrome in patients with ascites, and is frequently associated to the development of hepatic encephalopathy [1].

Finally, bacterial infection in patients with gastrointestinal bleeding is associated with increased hospital mortality. This impact on mortality has been demonstrated either directly or through its link with the severity of liver disease or of the bleeding episode [6, 40–43].

Clinical Impact of Different Prophylactic Strategies

Since most episodes of spontaneous bacterial infections in bleeding patients result from the translocation of enteric gram-negative bacilli, initial prophylactic strategies were focused on decreasing the concentration of these bacteria in the gut while preserving the protective anaerobic flora [29, 30]. Prophylaxis should also be safe and affordable. Norfloxacin, a poorly absorbable oral quinolone that eliminates selectively gram-negative bacilli from the intestinal flora, fulfills these criteria and has been broadly used in this setting. Other oral and/or systemic antibiotics (penicillins, cephalosporins, and other quinolones) have also been evaluated in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal bleeding (Table 10.1) [9, 26, 28–39]. The majority of the studies comparing antibiotic prophylaxis to placebo have shown a significant decrease in the incidence of bacterial infections in patients receiving antibiotics. Prophylaxis reduced the mean incidence of infections from 45 to 14 % (OR in favor of antibiotic prophylaxis: 4.64) [41, 43]. Other studies have compared two different antibiotics strategies (Table 10.1). These studies seem to suggest a higher efficacy of third-generation cephalosporins compared to quinolones or first-generation cephalosporins [26, 37–39]. However, a recent meta-analysis shows that all antibiotic strategies have a beneficial effect on bacterial infection, although the protective effect is stronger with cephalosporins and quinolones. Antibiotics prevent not only spontaneous infections (RR 0.25 for bacteremia and 0.29 for SBP) but also urinary infections (RR 0.23) and pneumonia (RR 0.45). Antibiotic prophylaxis also improves bleeding control and prevents rebleeding. Finally and more importantly, antibiotic prophylaxis is associated with a reduction in all-cause mortality (RR 0.79) and in mortality from bacterial infections (RR 0.35). Mean survival rate is around 85 % in patients treated with antibiotics and about 75 % in those not receiving prophylaxis [41, 43]. Table 10.2 shows the impact of different antibiotic strategies on clinical events other than infection in patients with cirrhosis and upper gastrointestinal bleeding.

Current Guidelines

Current guidelines establish that all cirrhotic patients with upper gastrointestinal bleeding should be considered for short-term prophylaxis of bacterial infections independently of liver function or of the presence of ascites [1, 15–17]. Table 10.3 shows the antibiotic strategies currently recommended according to the risk of infection.

Table 10.2 Impact of antibiotic prophylaxis on clinical events other than infection in patients with cirrhosis and gastrointestinal bleeding

Study	Clinical event
Trials comparing antibiotics with no intervention/placebo	
Rimola et al. [29]	No data
Soriano et al. [30]	No impact on mortality of antibiotic prophylaxis
	Lower cost of antibiotic therapy in the antibiotic prophylaxis group
Rolando et al. [31]	No data
Blaise et al. [32]	Lower mortality rate in the antibiotic prophylaxis group (24 % vs. 35 %)
Pauwels et al. [28]	Lower incidence of sepsis or shock (20 % vs. 67 %)
	Lower mortality rate (13 % vs. 24 %)
	Lower cost of antibiotic therapy in the antibiotic prophylaxis group
Hsieh et al. [33]	No data
Hong et al. [34]	Lower hospital cost and duration of hospitalization if antibiotic prophylaxis
	No differences in 30-day mortality (5 % vs. 5 %)
Lin et al. [35]	No differences in hospital mortality (0 % vs. 4 %)
Hou et al. [9]	Lower early rebleeding rate if antibiotic prophylaxis (8 % vs. 34 %)
	No differences in hospital mortality
Xu et al. [36][a]	Trend to lower early rebleeding rate in the antibiotic prophylaxis group
	No differences in hospital mortality
Trials comparing different antibiotics	
Sabat et al. [37]	No differences in mortality or in duration of hospitalization
Fernández et al. [26]	No differences in bleeding control, rebleeding, or mortality
Diaz et al. [38]	No differences in rebleeding or mortality
Wu et al. [39][a]	Higher rebleeding rate in Child-Pugh BC patients under cefazolin

[a]Retrospective study

Table 10.3 Current recommendations for antibiotic prophylaxis in variceal hemorrhage in cirrhosis

Risk	Antibiotic, route, and dose
Preserved liver function	Norfloxacin 400 mg/12 h PO for 7 days
Patients with advanced cirrhosis (at least two of the following: ascites, jaundice, hepatic encephalopathy, and malnutrition)	IV ceftriaxone 1 g/day during 7 days

Oral norfloxacin (400 mg/12 h for 7 days) is the gold standard prophylaxis in patients with preserved liver function. It is simple to administer and has a low cost. Potential limitations of oral norfloxacin are the following: (1) early infections caused by gram-positive cocci from respiratory tract and skin are not covered by this quinolone [26, 37]; (2) the oral route could be inappropriate in patients with active bleeding [28, 37]; and (3) norfloxacin is ineffective in patients colonized by quinolone-resistant *Enterobacteriaceae* [3, 4].

Patients with advanced cirrhosis (at least two of the following: ascites, severe malnutrition, encephalopathy, or jaundice) are at higher risk of infection and seem

to benefit more from the administration of systemic antibiotics than from intestinal decontamination. Guidelines suggest that this high risk population should receive IV ceftriaxone (1 g/day for 7 days) [1]. In a recent randomized controlled trial, the probability of developing proven or possible infections (11 % vs. 33 %, $p=0.003$), proven infections (11 % vs. 26 %, $p=0.03$), and SBP or spontaneous bacteremia (2 % vs. 12 %, $p=0.03$) was significantly lower in patients receiving ceftriaxone than in those under norfloxacin prophylaxis. Infections in the norfloxacin group were mainly due to quinolone-resistant gram-negative bacilli or non-enterococcal streptococci [26].

Independently of the liver function, patients with a history of recent infection by quinolone-resistant *Enterobacteriaceae* (3–6 months) should receive third-generation cephalosporins (ceftriaxone). Patients with recent infection by extended-spectrum β-lactamase-producing *Enterobacteriaceae*, in whom beta-lactams are ineffective, should be treated with antibiotics active against these multiresistant bacteria (e.g., oral nitrofurantoin 50 mg/6–8 h in patients with preserved liver function and IV ertapenem 1 g/day in patients with advanced cirrhosis) [44].

Antibiotic prophylaxis should be instituted as early as possible, ideally before or immediately after endoscopy according to a recommendation of the Baveno V consensus conference [1, 15]. A recent retrospective study has shown that timely administration of prophylactic antibiotics (before or within 8 h of endoscopy) is associated with reduced rebleeding rate (17 % vs. 29 %; OR: 0.27) and lower mortality (13 % vs. 35 %) [42].

Areas of Research

- Investigations focused on the specific mechanisms involved in the pathogenesis of bacterial translocation and infection in patients with cirrhosis and variceal bleeding are needed.
- New studies should evaluate alternative strategies to norfloxacin in patients with compensated cirrhosis and severe bleeding (hypovolemic shock or active bleeding).
- Non-antibiotic strategies and rifaximin should be compared to norfloxacin in cirrhotic patients with preserved liver function.
- Alternative antibiotics should be evaluated in patients with history of recent infections caused by multiresistant bacteria.

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Chapter 11
Use of Vasoactive Drugs for Acute Variceal Bleeding

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Introduction

Acute esophageal variceal bleeding is a severe complication of portal hypertension and a major cause of death in patients with hepatic cirrhosis [1]. In the last decades survival has been improved due to the implementation of effective treatments and optimization of general medical care but despite this standard of care, mortality is still closely related to failure to control hemorrhage or early rebleeding, and remains about 15–20 % in most recent series [2, 3]. The first approach to the bleeding patient is aimed at correcting hypovolemic shock and at preventing complications associated with gastrointestinal bleeding such as bacterial infections, hepatic decompensation, and renal failure, which require prompt management because they are associated with increased risk of rebleeding and death. The initial resuscitation should follow the classic Airway-Breathing-Circulation scheme, where it is important to avoid over-transfusion [4] by using a restricted blood transfusion policy (aimed at a hemoglobin level of about 7 g/dl) [5], infusion of plasma expanders and crystalloid solutions to keep systolic blood pressure around 100 mmHg [6]. In this scheme it is paramount to provide as soon as possible specific therapy aimed at controlling the bleeding, as continued bleeding increases dramatically the risk of deterioration of liver function and of multiorgan failure, leading to a situation where the patient survival no longer depends on controlling the bleeding itself [7].

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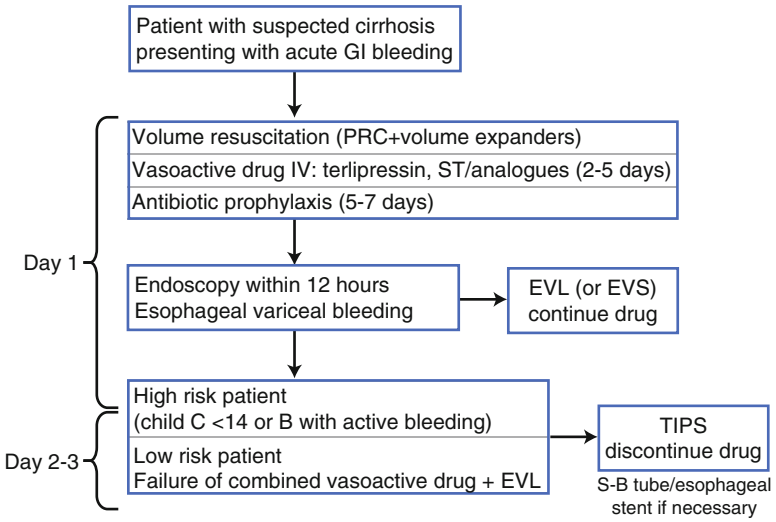

Fig. 11.1 Recommended treatment for acute bleeding from esophageal varices. Please note that volume resuscitation, vasoactive drugs, and antibiotic prophylaxis shall be initiated as soon as possible, in the emergency room. *ST* somatostatin, *EVL* endoscopic variceal ligation, *EVS* endoscopic variceal sclerotherapy, *TIPS* trans-jugular intrahepatic porto-systemic shunt, *S–B* Sengstaken–Blakemore

Current recommended standard of care for patients with acute variceal bleeding is a combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic procedures [8] (Fig. 11.1).

This chapter reviews the rationale for the use of drug therapy, its pharmacological and hemodynamic properties, and its clinical use, focusing on agents associated with an improved control of bleeding, decreased transfusion requirements, shorter hospital stay and decreased mortality, as well as its role in combination with endoscopic treatments and TIPS.

The Mechanism of Variceal Bleeding: Rationale for the Use of Vasoactive Drugs in Variceal Hemorrhage

Variceal bleeding is the last step of a chain that is initiated by the increase in portal pressure gradient, clinically evaluated as the hepatic vein pressure gradient (HVPG; normal values 1–5 mmHg). When the HVPG increases above 10 mmHg, the complications of portal hypertension may start to develop [9]; specifically, this is the minimum pressure gradient required for the formation of porto-systemic collaterals and esophageal varices, and for starting sodium retention [10, 11].

For esophageal variceal bleeding to develop, the varices shall increase in size and the HVPG shall increase further, to at least 12 mmHg, although mean HVPG values at the moment of bleeding are as high as 19 mmHg [12–14]. Brisk, repeated increases in portal pressure and blood flow prompted by meals [15, 16], physical exercise [17], increased intra-abdominal pressure [18, 19], and alcohol intake [20] are thought to be major determinants of this progressive dilatation of the varices [21]. In addition, as the varices dilate their walls become thinner, which is likely to be clinically evidenced by the appearance of red signs over the varices (red whales, red spots, and diffuse redness) [22]. It is widely accepted nowadays that the mechanism of variceal bleeding is the rupture of the varices when the tension exerted by its thin walls exceeds the elastic limit of the vessel ("variceal explosion" theory) [21]. Wall tension is the physical force generated by the variceal wall against the progressive expansion determined by increased intravariceal pressure, and is defined by the equation:

$$Tension = \left(Variceal\ pressure - Esophageal\ luminal\ pressure\right) \times Variceal\ radius\ /\ wall\ thickness$$

This equation indicates that increased variceal pressure plays a key role in determining bleeding. Furthermore, it points out that with equal variceal pressure, a large varix will have greater wall tension and risk of bleeding than one of smaller diameter, and that the same will happen for one with red color signs vs. one without. This is supported by a series of clinical studies measuring variceal pressure, diameter, and wall thickness in portal hypertensive cirrhotic patients [14, 23–25].

The role of increased portal pressure in variceal bleeding is not limited to be the initiating event that finally leads to variceal rupture. In addition, the amount of blood loss during bleeding is also determined by the magnitude of the portal/variceal pressure elevation, as factorized in the equation:

$$Blood\ loss = Intravariceal\ pressure \times Area\ of\ variceal\ rent$$

This is further modulated by two additional factors: decreasing blood viscosity (as caused by a drop in hematocrit) will increase blood loss, and the ability of the hemostatic mechanisms to achieve a plug at the bleeding site (which is mainly dependent of an adequate platelet number and function).

A pathophysiological approach to the treatment of variceal bleeding should therefore aim at decreasing variceal tension, and secondarily, at enhancing/maintaining primary hemostasis.

Decreasing variceal wall tension requires decreasing variceal pressure, which is a function of portal pressure, and variceal radius. This is only possible acutely by decreasing variceal blood flow, which is a function of portal-collateral blood flow. Thus, an ideal agent should be able to significantly reduce portal pressure and blood flow, which is essentially what is achieved by using agents causing splanchnic vasoconstriction. When effective, these agents will predictably result in decreased blood loss (and thus in smaller fall in hematocrit) and earlier and more

effective hemostasis at the bleeding point. An additional advantage of an effective splanchnic vasoconstrictor is that it will prevent "rebound" increases in portal/variceal pressure associated with blood volume restitution [26].

Available Agents: Vasoactive Drugs

Modern pharmacological agents for controlling variceal bleeding include somatostatin and its analogues and Terlipressin (Table 11.1). Other agents, such as vasopressin with or without nitroglycerin, are no longer used due to their side effects and will not be reviewed in detail [27].

Terlipressin (triglycyl lysine vasopressin) is a synthetic analogue of vasopressin that has a longer biological activity as compared to the original compound with fewer cardiac, bowel, and peripheral ischemic side effects and that rapidly reduces portal pressure through its splanchnic vasoconstriction activity [28–31]. Its administration leads to a decrease in cardiac output, an increase in the arterial blood pressure and the systemic vascular resistance, and to vasoconstriction of the splanchnic vascular circulation that altogether induce a decrease in portal pressure of about 20 % after a single injection [30]. It is usually administered by intermittent intravenous injections as its effects are still significant 4 h after administration (although continuous intravenous infusion is also possible) [31–33]. The currently recommended dose is of 2 mg every 4 h for the first 24–48 h (for adults over 40 kg of body weight); afterwards, the drug can be maintained for up to 5 days at a dose of 1 mg every 4 h to prevent early rebleeding and minimize side effects [34–36].

Table 11.1 Summary of the available pharmacological agents used in the treatment of acute bleeding from esophageal varices

Terlipressin
• Long-acting vasopressin analogue with higher affinity for vascular receptors
• Causes intense splanchnic vasoconstriction and increases arterial pressure
• Given IV as injections of 2 mp/4 h[a] for 24–48 h, then 1 mg/4 h for 2–5 days
• Well proven in placebo-controlled RCTs and meta-analysis
Somatostatin
• Very short biological half-life
• Causes moderate vasoconstriction due to glucagon inhibition and facilitation of adrenergic vasoconstriction
• Given as IV infusion of 250–500 μg/h, after an optional bolus of 250 μg, for up to 5 days
Somatostatin analogues (Octreotide, Vapreotide)
• Longer half-life
• Effects on portal pressure jeopardized by rapid desensitization
• Given as IV infusion of 50 μg/h, after an optional bolus of 50 μg, for up to 5 days
• Effective in RCTs when evaluated as an adjunct to endoscopic sclerotherapy

RCTs randomized controlled trials

[a]1 mg/4 h for subjects of <40 kg b.w.

As mentioned before, the side effects of Terlipressin are less common and severe than those of vasopressin but still can lead to treatment discontinuation. The most common side effect is abdominal pain, which reverses after drug withdrawal, and increases blood pressure. Serious side effects such as peripheral, intestinal, or myocardial ischemia occur in <3 % of the patients [35]. Because of the possibility to provoke ischemic complications and severe arrhythmias, terlipressin should not be used in patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease [37], and should be used with caution in the elderly and in hypertensive subjects.

During treatment with Terlipressin hyponatremia can be observed [38], especially in patients with a preserved liver function and with better response to treatment, and a few cases of neurological symptoms that reversed after drug interruption have been reported [37].

Somatostatin is a small peptide hormone that regulates the release of numerous secondary peptides. Its actions are mediated by G-protein coupled receptors (somatostatin receptor subtypes 1–5) that regulate ion channels and enzymes mediating the synthesis/degradation of intracellular second messengers including cyclic AMP, cyclic GMP, inositol triphosphate, and diacylglycerol [39]. While it has been shown that the administration of somatostatin in portal hypertensive patients induces splanchnic vasoconstriction and consequently reduces portal pressure [40], the exact mechanisms mediating this effect are incompletely understood. Among those that have been investigated, the inhibition of vasodilatory peptides and in particular of glucagon is the most important [41]. In addition, somatostatin facilitates adrenergic vasoconstriction and blocks the brisk increase in HVPG induced by meals and blood transfusion [42], which is considered a risk factor for rebleeding from portal hypertensive sources. A limitation of somatostatin is its short half-life ranging 1.2–4.8 min in patients with chronic liver disease [39]. Hence, in order to maintain an adequate plasma concentration, somatostatin should be administered by continuous IV infusion. A dose of 250 μg/h preceded by a 250 μg bolus (which can be repeated up to 3 times during the first hour) is effective in lowering the HVPG [27], but HVPG reduction is greater using a higher dose, of 500 μg/h [43], which is further associated with a marked and sustained decrease in collateral (azygos) blood flow. Studies during acute variceal bleeding have shown that the 500 μg/h dose is required to significantly reduce the HVPG in this setting [33], which is in keeping with the observation of a greater effectiveness of this dose when used to control variceal bleeding in high risk patients [44]. Major side effects are rare; minor side effects occur in about 21 % of patients and include vomiting and hyperglycemia that are usually easy to manage [39, 44].

Long-acting analogues of somatostatin have been developed to overcome the drawback represented by its short half-life [39]. These include Octreotide, Vapreotide, Lanreotide, and Seglitide; the latter has not been tested for portal hypertension. *Octreotide and vapreotide* acutely decrease portal pressure probably through a mechanism similar to that of somatostatin [39]. However, despite a longer half-life as compared to somatostatin, the duration of their hemodynamic effects on

portal pressure is not longer, and continuous infusion or repeated injections have much less marked effects on portal pressure [45] probably due to the rapid development of desensitization or tachyphylaxis. In any case, Octreotide is effective in preventing the postprandial splanchnic hyperemia in portal hypertensive patients [46, 47], and this effect is long-lasting [47, 48]. Octreotide and vapreotide are usually given in continuous infusion of 50 μg/h with an optional initial iv or subcutaneous bolus of 50 μg. These doses are empirical since no formal dose response studies have been conducted in portal hypertensive subjects.

Clinical Use of Available Drugs

As discussed previously, vasoactive drugs exert their action by reducing portal pressure mostly by reducing splanchnic blood flow; this results in lowering gastroesophageal varices pressure and wall tension, better control of hemorrhage, and easier performance of endoscopy. Therefore, therapy with vasoactive drugs should be started as soon as possible, before endoscopy [8] in order to facilitate the procedure by reducing the rate of active bleeding and furthermore the rebleeding rate. Terlipressin was even used during ambulance transfer to hospital in a placebo-controlled clinical trial that indeed demonstrated improved control of bleeding and survival [49, 50]. Indeed, treatment with vasoactive drugs alone is able to control bleeding in up to 83 % of patients [51].

Terlipressin is considered the drug of choice in this setting, since it significantly improves control of bleeding as compared to placebo [50]. It is the only drug, up to date, that has been shown to improve survival as compared to placebo in individual trials and meta-analysis, so there is robust evidence for its use [49, 50]. Terlipressin has been compared to somatostatin in two trials, showing similar results of the two drugs in terms of control of bleeding [52, 53]. Its overall efficacy in controlling acute variceal bleeding has been reviewed in a meta-analysis [50], resulting of 75–80 % at 48 h and of 67 % at 5 days across trials. The reduction in all causes mortality risk induced by Terlipressin as compared to placebo was of 34 % (RR 0.66; 95 % CI 0.49–0.88), and was mainly attributed to a significant reduction in the failure to control bleeding (RR 0.63; 95 % CI 0.45–0.89) [50]. An additional advantage of Terlipressin is that its use may prevent the onset of the hepatorenal syndrome, which is sometimes precipitated by bleeding, as Terlipressin is also effective for the hepatorenal syndrome [54].

With regard to *somatostatin and its analogues*, a randomized trial demonstrated that somatostatin added to endoscopic therapy significantly improves the control of acute variceal bleeding when compared to placebo (63 % vs. 46 %), but does not improve survival [2]. Placebo-controlled trials of somatostatin vs. placebo as single agent yielded divergent results [2]. It should be underlined that in a study comparing two doses of somatostatin in patients with acute variceal bleeding (standard dose,

250 μg/h vs. high dose, 500 μg/h) [44] the rate of control bleeding was significantly higher in the subgroup of high-risk patients treated with a high dose, and the survival increased in this subgroup, suggesting that this dose should be preferred in patients at high risk of treatment failure [8, 13, 55]. Both somatostatin and octreotide had equal efficacy on the control of bleeding as endoscopic sclerotherapy, with a lower rate of side effects [2, 56]. Even if *octreotide* has not been evaluated in this setting in double-blind randomized trials vs. placebo (only one has been presented in abstract form, with negative results) [57], a meta-analysis of its effects in combination with endoscopic therapy suggests that it improves the control of bleeding without impacting mortality [58]; however, the strength of this evidence is limited and should be interpreted with caution [59]. *Vapreotide and lanreotide* have been used in trials in combination with endoscopic treatment; while vapreotide was reported to be better than placebo in a randomized controlled trial [60], a large trial involving lanreotide gave negative results and remained unpublished.

Selection of the Drug

According to what was stated previously, Terlipressin is the drug of choice in patients with acute variceal bleeding and without contraindications, due to its ability of improving survival [49, 50]. Nonetheless, as in any other setting in medicine, the selection of the drug depends on the local resources and Terlipressin is not available in all countries. Remarkably, octreotide is the only vasoactive drug for variceal bleeding control available in the United States.

Somatostatin, especially when used at high dose, appears to be as effective as terlipressin although an effect on survival has never been confirmed out of the subgroup analysis of high risk patients receiving high-doses of somatostatin [44]. It represents a reasonable alternative [8], taking into account its excellent safety profile. The somatostatin analogues octreotide and vapreotide can be used, especially where somatostatin and terlipressin are not available. In some countries, the combination of vasopressin infusion (0.2–0.4 U/min) plus transdermal nitroglycerin is still used [8].

Duration of the Treatment

According to current recommendations [8], vasoactive drugs should be used in combination with endoscopic therapy and continued for up to 5 days, since this frame time identifies the period at higher risk of rebleeding. However, there are limited and conflicting data to show the best treatment duration when drug therapy is used together with endoscopic band ligation, as it is currently recommended. In this situation the minimal duration of drug therapy should be until achieving a

24 h bleeding-free period, although in our hospital if there are no adverse effects we continue therapy until day 5.

Conclusions

Vasoactive drugs are the first-line therapy in acute variceal bleeding and should be administered from arrival to hospital or even during ambulance transfer, since treatment with these agents before endoscopy has been shown to ameliorate patient's outcome and allows a safer endoscopic procedure. The choice of the specific drug has to be done according to each center possibilities but when available terlipressin is the best option.

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Chapter 12
Endoscopic Treatment of Acute Variceal Bleeding

Christos Triantos, Maria Kalafateli, and Andrew Kenneth Burroughs

Introduction

Acute variceal bleeding (AVB) is a clinical emergency requiring high dependency care and sometimes direct admission to an intensive care unit. The incidence of AVB in patients with cirrhosis ranges between 5 and 15 % [1] and is associated with 6-week mortality rates of approximately 20 % [2, 3]. The major predictive factors of the first variceal bleeding episode are the size of varices, the severity of liver disease, the endoscopic presence of red wale marks [4] and a hepatic venous pressure gradient (HVPG) greater than 20 mmHg [5]. The use of prophylactic antibiotics has improved survival, supporting evidence for the role of bacterial infections on triggering variceal rupture and bleeding [6]. In a recent study [7], 102 patients with AVB were classified into two groups according to the severity of cirrhosis, group A (51 patients with Child-Pugh A stage) and group B (51 patients with Child-Pugh B and C stages) aiming to compare the outcome of intravenous cefazoline and ceftriaxone as prophylactic antibiotics. No significant difference in the prevention of infection between cefazoline and ceftriaxone was shown among group A patients (93.1 % vs. 90.9 %, $p=0.641$); however, in group B a trend in favour of ceftriaxone prophylaxis was observed (77.8 % vs. 87.5 %, $p=0.072$). The rate of rebleeding was higher in patients who received cefazoline than in those who received ceftriaxone among group B patients (66.7 % vs. 25 %, $p=0.011$), but no difference was observed in group A (32 % vs. 40.9 %, $p=0.376$). Apart from prophylactic antibiotics, the advances in endoscopic techniques have also contributed to the reduced mortality rates.

The combination of endoscopic and pharmacological treatment is by consensus [8] the most effective approach for bleeding varices. In patients with upper gastrointestinal

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bleeding and a suspicion of cirrhosis, pharmacological agents should be initiated as soon as possible after admission and continued for up to 5 days, whereas endoscopy should be performed within 12 h.

In this chapter, we evaluated randomized clinical trials (RCTs) and prospective studies for the endoscopic management of AVB; meta-analytical data were used, when applicable, aiming to report the most recent advances in the endoscopic treatment of bleeding varices. We searched MEDLINE database, Scopus and Web of Knowledge search system from July 1968 until June 2013 using the text words "acute variceal bleeding", or "management and variceal bleeding" or "endoscopy and variceal bleeding". The criteria used to retrieve studies were: (a) study type of either randomized controlled trial, clinical trial, case-report or meta-analysis, (b) a published abstract or article, (c) feasible translation to English and (d) study population of patients with variceal bleeding due to cirrhosis (gastric, oesophageal or gastroesophageal).

Timing of Endoscopy

Chen et al. [9] found that door-to-endoscopy time, MELD score and portal vein thrombosis were associated with 6-week rebleeding, while haematemesis upon arrival, MELD score and hepatocellular carcinoma (HCC) were associated with 6-week mortality. In patients with haematemesis, 6-week rebleeding (18.9 % vs. 38.9 %, $p=0.028$) and mortality (27 % vs. 52.8 %, $p=0.031$) were lower in those with early (≤12 h) rather than delayed endoscopy. The significance of early endoscopy in predicting mortality in AVB was also supported by the analysis of the United States' Nationwide Inpatient Sample [10]. In this study, risk factors for increased mortality were age >60, African American race, comorbidities, insurance type and delayed esophagogastroduodenoscopy (EGD). Endoscopy within one day of admission was more likely in men, White Americans, patients aged 18–40 years, privately insured and those with no comorbidities. In another study with 311 patients with AVB [11], delayed endoscopy for more than 15 h (adjusted OR 3.67, 95 % CI 1.27–10.39) together with high MELD score (adjusted OR 1.16, 95 % CI 1.07–1.25), failure of the first endoscopy (adjusted OR 4.36, 95 % CI 1.54–12.3) and haematemesis (adjusted OR 8.66, 95 % CI 1.06–70.9) was an independent risk factor for in hospital mortality in patients with cirrhosis and AVB. However, in 210 patients with haemodynamically stable AVB, there was no significant association of time to endoscopy with mortality (OR 1.0; 95 % CI 0.92–1.08, $p=0.91$), whereas significant independent associations with mortality were lower albumin (OR 0.82, 95 % CI 0.73–0.93, $p=0.001$), infection during admission (OR 8.9, 95 % CI 2.5–31.6, $p<0.001$) and higher MELD score (OR 1.17, 95 % CI 1.06–1.29, $p=0.002$) [12]. However, the results of this study were debatable considering its retrospective design and the fact that the urgency of endoscopy was more likely in patients who presented with haematemesis or had endoscopic stigmata, and thus more severe bleeding [13].

Endoscopic Treatment Versus Vasoactive Drugs

In a recent Cochrane meta-analysis of 17 trials (14 published as full reports, 3 as abstracts) including 1,817 patients [14], the efficacy of vasoactive drugs (vasopressin with/without nitroglycerin, terlipressin, somatostatin or octreotide) versus emergency sclerotherapy was assessed. No significant differences were found comparing sclerotherapy with each vasoactive drug for any outcome (failure to control bleeding, 5-day treatment failure, rebleeding, mortality, number of blood transfusions and adverse events). Combining all the trials irrespective of the vasoactive drug, the risk differences (RD) were −0.02 (95 % confidence intervals (CI) −0.06 to 0.02) for failure to control bleeding, −0.05 (−0.10 to 0.01) for 5-day treatment failure rate, 0.01 (95 % CI −0.03 to 0.05) for rebleeding, −0.02 (95 % CI −0.06 to 0.02) for mortality and −0.24 (95 % CI −0.54 to 0.07) for transfused blood units. Adverse events (RD 0.08 (95 % CI 0.03–0.14)) and serious adverse events (RD 0.05 (95 % CI 0.02–0.08)) were significantly more frequent with sclerotherapy than with pharmacological treatment. Emergency injection sclerotherapy is not superior to vasoactive drugs for the treatment of AVB and was associated with a higher incidence of complications.

In an RCT [15], patients with AVB were randomized to undergo either emergency endoscopic variceal ligation (EVL, $n=62$) or receive somatostatin ($n=63$) for 48 h. Treatment failure rate was 4.8 % in the EVL group and 31.7 % in the somatostatin group ($p=0.0001$), with fewer transfusion requirements ($p=0.03$) and a tendency for shorter hospital stay ($p=0.07$) in the EVL group. However, there were no differences between groups regarding 42-day mortality and adverse events.

Endoscopic Treatment Plus Vasoactive Drugs Versus Vasoactive Drugs

Five RCTs [16] including 400 patients have investigated the efficacy of emergency sclerotherapy combined with vasoactive agents (vasopressin, somatostatin or octreotide) compared to vasoactive drugs alone. The group receiving combination treatment demonstrated significantly less frequent failure to control bleeding with a pooled difference of 16.3 % (95 % CI 8.7–23.9 %, $p=0.0001$). A 5.5 % survival difference (95 % CI −1.8 to 12.7 %) was found favouring the combination group versus the monotherapy group, but this difference did not reach statistical significance ($p=0.138$).

A RCT [17] studying the efficacy and safety between EVL combined with octreotide ($n=51$) and octreotide monotherapy ($n=50$) showed that treatment failure (defined as active bleeding 72 h after treatment, not completion of EVL procedure or death) was lower in the combination group than in the octreotide monotherapy group (10 % vs. 26 %, $p<0.05$) together with lower transfusion requirements and shorter hospital stay.

Endoscopic Treatment Versus Endoscopic Treatment Plus Vasoactive Drugs

A meta-analysis of eight RCTs with 1,026 patients [16] has shown that the combination of sclerotherapy with vasoactive agents is superior in controlling bleeding compared with sclerotherapy alone with a difference of 13.2 % (95 % CI 8.4–18.1 %, $p<0.001$), but there was no difference in survival (pooled difference 3.4 % (95 % CI −0.4 to 7.1 %, $p=0.08$)).

In a meta-analysis [18] of eight trials involving 939 patients, combined treatment (endoscopic combined with somatostatin, octreotide or vapreotide) compared to endoscopy alone (sclerotherapy or EVL) improved initial control of bleeding (relative risk 1.12, 95 % CI 1.02–1.23), and 5-day haemostasis (relative risk 1.28, 95 % CI 1.18–1.39), with a number needed to treat of 8 and 5, respectively. The difference in favour of combined treatment remained significant, when trials that used drugs other than octreotide, or that included a low proportion of alcoholic patients (<40 %) or high-risk cirrhotic patients (<35 % of Child-Pugh C patients) were excluded. Mortality was not significantly decreased by combined therapy (relative risk 0.73, 95 % CI 0.45–1.18). Severe adverse events were similar in both groups.

Sclerotherapy Versus Variceal Ligation

A meta-analysis of 12 RCTs comprising 1,309 patients [16] showed that EVL was significantly better for control of bleeding compared to sclerotherapy, but the difference was only 2.5 % (95 % CI 0.4–4.6 %, $p=0.018$). Regarding mortality, the percentage difference was 1.3 % favouring ligation, but this difference was not statistically significant ($p=0.46$). None of the trials had the combination of vasoactive drugs with either endoscopic technique. Villanueva et al. [19] randomized patients with AVB receiving intravenous somatostatin to EVL ($n=90$) or injection sclerotherapy ($n=89$). Failure to control bleeding occurred in 15 % with sclerotherapy and in 4 % with ligation ($p=0.02$). Ligation resulted in a higher 6-week survival rate than sclerotherapy (83 % vs. 67 %, $p=0.01$) Complications occurred in 28 % patients receiving sclerotherapy and 14 % with EVL ($p=0.03$), and the rate of major side-effects was also higher in the sclerotherapy group (relative risk 3.1, 95 % CI 1.1–9.1, $p=0.04$). In the subgroup of patients with active bleeding, therapeutic failure was not significantly different (sclerotherapy: 5/21 (28 %) vs. EVL: 3/17 (18 %); relative risk 1.3, 95 % CI 0.4–4.8). In an RCT by Avgerinos et al. [20] in AVB, a sustained rise of portal pressure was observed with injection sclerotherapy ($n=25$) with HVPG remaining high during the 120-h study period, whereas with EVL ($n=25$), HVPG returned to baseline values within 48 h ($p<0.0001$). The rebleeding rate was lower with EVL compared to sclerotherapy (12 % vs. 40 %, $p=0.024$) during the 42-day follow-up. EVL is by consensus [8] the recommended endoscopic approach, although sclerotherapy could be used in the acute setting if ligation is technically difficult.

Other Endoscopic Approaches in the Setting of Acute Variceal Bleeding

In an RCT [21], patients with recent or AVB were randomly assigned to modified percutaneous transhepatic varices embolization (PTVE) with 2-octyl cyanoacrylate ($n=52$) or EVL ($n=50$). Eight patients treated with PTVE and 21 patients treated with EVL developed recurrent upper gastrointestinal bleeding during the follow-up period ($p=0.004$): recurrent oesophageal variceal bleeding occurred in 3 and 12 patients in the PTVE and EVL groups, respectively (relative risk 0.24, 95 % CI 0.05–0.74, $p=0.012$). However, there were no significant differences in survival between groups.

Tissue adhesives have also been used endosopically in oesophageal AVB. In a prospective cohort study [22] of 133 cirrhotic patients with bleeding oesophageal varices (52 with active and 81 with recent bleeding), undiluted *N*-butyl-cyanoacrylate (NBC) achieved initial haemostasis in 49 (94.2 %) active bleeders. Early rebleeding occurred in 7 patients (5.2 %) and 6-week mortality was 8.2 %. and no major procedure-related complications were recorded. In an RCT [23], conventional sclerotherapy was compared to NBC injection which was superior to sclerotherapy for both reduction in rebleeding (11.1 % vs. 55.6 %, $p=0.01$) and mortality (33.3 % vs. 72.2 %, $p=0.04$) rates. The efficacy of combined treatment with sclerotherapy and NBC was compared to sclerotherapy alone in two RCTs [24, 25]. In the study by Feretis et al. [24], the combination treatment had lower rebleeding rate (2/20) than the sclerotherapy alone (8/18, $p<0.05$). In hospital mortality rate was also lower with combination treatment (3 of 21 vs. 9 of 18, $p<0.05$). In the second RCT [25], the results were similar with the combination treatment resulting in less rebleeding (8.6 % vs. 25 %, $p<0.01$), less minor complications and reduced mortality (3.5 % vs. 8.8 %, $p<0.05$). In a recent RCT [26], patients with oesophageal AVB were randomized to receive either EVL ($n=21$) or endoscopic injection with NBC ($n=22$). Both treatments had the same efficacy regarding initial haemostasis and transfusion requirements. The rebleeding rate was higher with NBC than with ligation (13.6 % vs. 4.7 %), but not significantly so ($p=0.6$). Mortality rates were also similar between groups (NBC: 45.5 % vs. EVL: 33 %, $p=0.327$).

Endoloops are detachable nylon snares and animal studies have shown that endoloop ligation is more effective in initial haemostasis for varices of 3–5 mm than band ligation or injection sclerotherapy [27]. In a prospective non-randomized study [28], 25 patients with oesophageal AVB were treated with elastic band ligation and 25 with endoloop ligation. The recurrence of bleeding during a follow-up of 6 months was smaller with endoloop ligation (12 %) compared to band ligation (28 %), but this difference was not significant. Furthermore, no differences were found between groups with respect to the number of patients with variceal eradication, the number of treatment sessions required for variceal eradication, or the frequency of variceal recurrence. However, use of the endoloop had resulted in a better field of vision, tighter application, good results with junctional varices, and a lack of strain exerted by the device on the endoscope compared to EVL.

Endoscopic clipping of oesophageal varices has been introduced as an alternative in variceal eradication. In a prospective non-randomized study [29], 19 patients presented with AVB were treated with endoscopic clipping and 21 with band ligation. All patients treated by clipping and 19 of 21 treated by banding achieved initial haemostasis. Variceal eradication was achieved in 89 % and 76 % of patients treated by clipping and banding ligation, respectively, but this difference was not significant ($p > 0.05$). However, the median number of sessions needed for variceal eradication was lower in the clipping group (3 vs. 4, $p = 0.013$). No difference was observed regarding rebleeding rate between the two groups (15 % vs. 33 %, $p > 0.05$). In another small, single-centre prospective trial [30], haemoclipping achieved initial control of variceal bleeding in 32 of 34 (94 %) patients and the rates of variceal recurrence, rebleeding and mortality were 16 %, 9 % and 12 %, respectively, suggesting that clipping is probably as efficacious as banding ligation. It remains for RCTs to confirm these results.

The data on the efficacy and safety of laser treatment in AVB is scarce. In an old RCT [31], 10 patients with AVB were randomized to laser treatment (endoscopic neodymium:yttrium aluminium garnet (Nd:YAG)) and 10 patients to a control group (sham endoscopy and standard medical treatment). Initial haemostasis was achieved in 7 laser-treated patients but in none of the controls ($p < 0.002$). However, 4 of 7 with initial haemostasis with laser treatment rebled 12–48 h later. The mean blood transfusion requirements were similar in both groups. Four patients treated by laser and 7 controls died during hospitalization but this difference was not significant ($p = 0.22$). Laser therapy increased bleeding by 20 % but no perforations were observed.

In a small RCT [32], endoscopic treatment with human-derived fibrin glue was found superior to sclerotherapy with polidocanol regarding rebleeding, survival and incidence of complications. However, more experience is needed in order to confirm the efficacy of these alternative endoscopic procedures considering the safety issues that accompany the use of these techniques.

Predictors of Early Rebleeding and Mortality

Uncontrolled bleeding (defined as “variceal bleeding that cannot be controlled or recurs early—within 5 days—despite the initial pharmacological and endoscopic treatment” [33] is associated with the severity of liver disease (assessed by Child-Pugh classification), active bleeding at endoscopy, presence of HCC, shock at admission, non-alcoholic aetiology of cirrhosis and an HVPG greater than 20 mmHg [34]. Predictors of 6-week mortality are failure to control bleeding within 5 days, Child-Pugh grade C, concomitant HCC, shock at admission and HVPG > 20 mmHg [34]. Among patients with AVB at different stages of liver disease treated with antibiotics, somatostatin and endoscopic ligation, Child-Pugh C patients with baseline creatinine levels <1 mg/dL seem to have similar mortality to Child-Pugh A and B patients, whereas Child-Pugh C class with creatinine ≥1 mg/dL is associated with

a higher mortality rate [35]. In a recent study [36] aiming to assess the risk factors for in-hospital mortality in patients with variceal bleeding, transfusion with ≥2 packed red blood cells, MELD >18 and platelets ≤100/mL were significantly associated with in-hospital mortality in the multivariate analysis, but the area under the curve derived from the multivariate model was only 0.76 (95 % CI, 0.64–0.88).

Gastric Variceal Bleeding

The available data on the management of AVB from gastric varices is far more limited than that of oesophageal variceal bleeding. The incidence of bleeding from gastric varices is approximately 25 % in 2 years [37] and compared to oesophageal variceal bleeding is associated with higher transfusion requirements and higher rebleeding and mortality rates [37]. Predictive factors for bleeding gastric varices are the size of the varix, the severity of liver disease and the endoscopic presence of red spots on variceal surface [38]. Type 1 gastroesophageal varices (GOV) are an extension of oesophageal varices along the lesser curvature of the stomach, whereas type 2 GOV extend along the fundus. Isolated gastric varices (IGV) are categorized into type 1 IGV which are located in the fundus and Type 2 IGV which can be found everywhere else in the stomach [37].

Endoscopic Glue Injection

The management of bleeding from type 1 GOV is the same as for oesophageal variceal bleeding. However, the best therapeutic approach for acute bleeding from IGV and type 2 GOV is, by consensus [8], endoscopic treatment with tissue adhesives such as NBC. In an RCT [39] of 37 consecutive patients with IGV type 1 (acute and recent bleeding), endoscopic treatment with alcohol injection ($n=17$) or cyanoacrylate glue was compared for variceal obliteration, rebleeding and mortality. The cyanoacrylate was significantly more effective in achieving variceal obliteration than alcohol (100 % vs. 44 %). Cyanoacrylate injection achieved control of bleeding more often (89 % vs. 62 %), but this difference was not significant. Moreover, mortality was not different between groups (alcohol: 29.4 % vs. cyanoacrylate: 10 %, $p=$ns). In another prospective RCT [40] in patients with cirrhosis and gastric variceal bleeding, the efficacy and complications of EVL ($n=29$) and endoscopic NBC injection ($n=31$) were compared. Active bleeding was present in 15 patients with NBC and in 11 patients with EVL, whereas the initial haemostatic rate was 87 % versus 45 %, respectively ($p=0.03$). EVL resulted in a higher rebleeding rate (54 %) compared to NBC (31 %) ($p=0.0005$). Transfusion requirements were also higher with EVL (4.2 ± 1.3 vs. 2.6 ± 0.9 units, $p<0.01$). Mortality rates were 29.03 % (NBC) and 48.3 % (EVL) ($p=0.05$). Tan et al. [41] also conducted an RCT of EVL ($n=48$) versus NBC injection ($n=49$). Both endoscopic therapies had the same

efficacy in controlling active bleeding (14/15 vs. 14/15, $p=1.00$). Gastric variceal rebleeding was more frequent with EVL (21/48) versus NBC (1/49, $p=0.044$). The 2- and 3-year cumulative rates of rebleeding were 63.1 % and 72.3 % for EVL and 26.8 % for both periods with NBC injection (log rank test, $p=0.143$). In multivariate Cox regression analysis, the presence of HCC (relative hazard 2.453, 95 % CI 1.036–5.806, $p=0.041$) and EVL (relative HR 2.660, 95 % CI 1.167–6.061, $p=0.02$) were independent associations with rebleeding. However, there were no differences in survival between groups. Advanced liver disease is another predictive factor for rebleeding in patients with acute gastric variceal haemorrhage treated with NBC injection [42]. In a retrospective trial [43], cyanoacrylate injection ($n=61$) was compared to TIPS ($n=44$) as first-line treatments in bleeding gastric varices. There were no significant differences in 72-h, 3-month and 1-year rebleeding, overall survival or acute complications between groups, but TIPS had a higher rate of long-term morbidity requiring hospitalization (41 %) compared to cyanoacrylate (1.6 %, $p<0.0001$). However, the validity of these results is limited by the lack of randomization.

The use of 1.0 mL of cyanoacrylate injection ($n=47$) does not have better haemostatic efficacy than 0.5 mL ($n=44$) with no differences in treatment failure, complications, 30-day mortality and survival [44], although larger RCTs are needed to determine if the larger dose is more efficacious. The use of adjuvant hypertonic glucose solution in 67 patients with successful initial obliteration of gastric varices with tissue adhesives reduced the recurrence or progression of gastric varices and, thus, the risk for rebleeding [45], but this also needs to be clarified by larger RCTs.

Thrombin Injection

Human thrombin injection therapy forms a fibrin clot at the needle tip immediately upon injection and is another alternative to tissue adhesives with high rates of initial haemostasis with the benefit of being safer but the rebleeding rate exceeds 10 % (4 of 33 patients with bleeding gastric varices) [46].

TIPS

TIPS is the best treatment option in patients with rebleeding or uncontrolled gastric variceal bleeding. In a prospective trial [47], the efficacy of salvage TIPS in patients with uncontrolled oesophageal ($n=84$) versus gastric fundal variceal bleeding ($n=29$) was compared. Initial control of bleeding was achieved in all but one patient in each group. Rebleeding occurred in 24 % in the group of oesophageal varices and in 29 % in the group of gastric varices during a median follow-up of 7 months and mortality was the same between the two groups.

Balloon-Occluded Retrograde Transvenous Obliteration

Considering the high rebleeding rate of endoscopic variceal obliteration with cyanoacrylate injection, balloon-occluded retrograde transvenous obliteration (B-RTO) has been developed in Japan as a reliable therapeutic method for the prevention of primary bleeding from high-risk gastric varices and of secondary bleeding of gastric varices [48]. The 5-year rebleeding rate after B-RTO in patients following gastric variceal bleeding was 0–5.5 % [48]. However, these results are from small prospective studies and RCTs are needed in order to clarify the efficacy of B-RTO in the setting of gastric variceal bleeding.

Complications of Endoscopic Procedures

Safety

Diagnostic EGD in non-bleeding patients is a safe procedure. However, in cases of emergency, such as AVB, the incidence of complications of EGD increases from 0.7 to 8 %: these complications are mostly cardiopulmonary [49]. Aspiration, a major contributor to the cardiopulmonary complications, can be frequent in AVB at a rate of approximately 2.4 % (18 of 741) of patients with index bleeding, increasing to 3.3 % in cases of rebleeding, due to the presence of blood inside the stomach [50]. Endotracheal intubation is commonly used for airway prophylaxis prior to endoscopy to obviate this complication. In a retrospective study [49], 42 patients with AVB who underwent elective intubation were compared to 20 patients who were not intubated. Patients who were not intubated had similar demographic characteristics, but a significantly higher CP score and a lower rate of EVL versus sclerotherapy compared to intubated patients. Pulmonary infiltrates developed in 7 (17 %) intubated patients with an overall mortality rate of 21 % and in none of the non-intubated patients with 5 % overall mortality regardless of the presence of haematemesis or active bleeding at endoscopy. These results are counter-intuitive and the study requires prospective validation. However, EVL requires reinsertion of the endoscope after diagnosis of variceal bleeding and places patients at a further risk for aspiration; the results may be explained by this. Contrasting results were reported by Rudolph et al. [51] who compared outcomes during 2 separate years for intensive care unit patients with upper gastrointestinal bleeding during 1988 during which prophylactic endotracheal intubation was seldom performed before endoscopy, with outcomes during 1992 in which endotracheal intubation was routine for airway protection before or during EGD. Patients in 1988 ($n=101$) and 1992 ($n=119$) were comparable with respect to number of patients who had shock (66.3 % vs. 67.2 %), cirrhosis (34.7 % vs. 38.6 %), variceal/portal hypertensive bleeding (22.8 % vs. 33.6 %) and endoscopic therapy (37.6 % vs. 42.0 %). There were no significant differences in endotracheal intubation at any time during hospitalization (24.8 % vs. 28.6 %), in all

EGD-related cardiopulmonary complications (5.0 % vs. 3.4 %), in new pulmonary infiltrates after EGD (12.9 % vs. 15.1 %), in mean number of intensive care unit days (7.1 vs. 6.4) or in mortality (15.9 % vs. 11.8 %) between the 1988 and 1992 cohort of patients. New infiltrates were developed in 10 (48 %) of 21 patients after EGD, despite endotracheal intubation specifically used for airway protection. However, in 1992 there were no fatal episodes of aspiration during EGD (2.0 % vs. 0 %; $p=0.21$), no emergency complications following endotracheal intubation (6.0 % vs. 0 %; $p<0.05$), and fewer in-hospital cardiopulmonary arrests (12.9 % vs. 5 %; $p<0.05$).

Sclerotherapy

Endoscopic variceal eradication has been associated with oesophagus motility abnormalities and gastroesophageal reflux but the exact mechanism remains poorly understood [52]. An RCT [53] of 73 cirrhotic patients with one episode of variceal bleeding controlled by one session of endoscopic treatment were randomized either to sclerotherapy ($n=37$) or EVL ($n=36$). Sixty patients (30 in each group) underwent oesophageal manometry and 24-h intra-oesophageal pH monitoring at inclusion and 1 month after variceal eradication. After sclerotherapy, peristaltic wave amplitude decreased from 76.2 ± 14.7 to 61.6 ± 17.7 mmHg ($p=0.0001$), simultaneous contractions increased from 0 to 37.9 % ($p=0.0008$) and the percentage of time with pH <4 increased from 1.60 ± 0.25 to 4.91 ± 1.16 % in channel 1 ($p=0.0002$) and from 1.82 ± 0.27 to 5.69 ± 1.37 % in channel 2 ($p=0.0006$). Ligation was not associated with such disturbances. Sclerotherapy has also been associated with a 5–10 times greater incidence of transient bacteremia (17.2 % vs. 3.3 %) and infectious complications (18 % vs. 1.8 %) compared to EVL following control for AVB [54]. Other adverse events that accompany sclerotherapy are ulcers with the probability of bleeding, and after long-term treatment oesophageal stenosis [14].

Endoscopic Variceal Ligation

EVL is safer than sclerotherapy and is mainly associated with minor complications including retrosternal pain, transient dysphagia or fever [55]. However, in EVL, diagnostic endoscopy has to be done first to evaluate the source of bleeding. If oesophageal varices are the source, a double intubation is needed in order to place the ligation device, thus increasing the risk for aspiration and the duration of the procedure [56]. Post-banding oesophageal strictures occur at a rate of 1.9 % [57]. Following EVL, oesophageal ulcers are commonly found due to ischaemic necrosis following strangulation leading to band detachment [58]. Compared with sclerotherapy-related ulcers, these tend to be smaller, more superficial, less likely to bleed, and quicker to heal [59]. Rebleeding from post-band ulcers is a rare complication which occurs in cases of early detachment of the band [60].

Iatrogenic bleeding has raised the issue of safety of EVL especially in the setting of primary prophylaxis of variceal bleeding [61–63]. In one recent study [64], 21 of 605 (3.5 %) patients developed post-banding bleeding due to spontaneous band slippage on post-banding ulcer. Post-banding bleeding related mortality was 52 % mainly because of the development of sepsis. Using a multivariate analysis, previous upper variceal bleeding (OR 12.07, 95 % CI (2.3–63.43)), peptic oesophagitis (OR 8.9, 95 % CI (1.65–47.8)), high platelet ratio index (APRI) score (OR 1.54, 95 % CI (1.11–2.16)) and low prothrombin index (OR 0.54, 95 % CI (0.31–0.94)) were independent predictive factors of post-banding bleeding occurrence. The first developed version of band ligator was only able to deliver one band at a time and thus, required repeated reloading and reinsertion of the device into the oesophagus [65]. Thus, there were oesophageal tears and perforation due to the repeated insertion of the endoscope and the use of an overtube to avoid de novo intubation [66]. The use of the overtube was also associated with tracheal compression, mucosal lacerations and haematomas [67]. This risk was lowered by the development of multi-band ligators which eliminated the need for overtube placement [66]. The main drawback of multi-band ligators is the limited endoscopic field of view [66]. Considering the number of bands placed per session to achieve variceal obliteration, an RCT [68] showed that the placement of >6 bands per session is not associated with better patient outcomes, but with significantly more prolonged banding and total procedure times and significantly more misfired bands compared with a maximum of six bands per session. Some reports [69] suggest that EVL is similar to sclerotherapy, increases the risk of developing or worsening pre-existing portal hypertensive gastropathy and is associated with the formation of fundal varices. However, no significant variation in portal pressure or worsening of portal hypertensive gastropathy or development of fundal varices has been observed [70].

Endoscopic Glue Injection

Complications of endoscopic glue injection can be either local or systemic. Local complications include giant ulcerations at the site of injection, bleeding from the site of injection during the procedure, which on occasion is uncontrolled especially in patients with high risk gastric varices (large, with red spots in Child-Pugh C patients). Early rebleeding is associated with early extrusion of the glue cast within 7 days from the procedure, and late rebleeding due to incompletely eradicated gastric varices at any time during follow-up [71]. Systemic complications include transient fever and bacteremia, as well as thrombus formation on the plug surface which can be colonized by bacteria which may embolize leading to abscesses in distant organs [71]. Pulmonary embolism from the injected material is reported with an incidence of approximately 1 %, and can be fatal [72]. Embolic complications in other large veins including superior mesenteric, splenic portal or renal veins have also been reported in case reports [71]. Factors contributing to these thromboembolic events are the presence of large gastric varices with high-flow shunts,

which are common in patients with cirrhosis, the existence of vascular malformations, the dilution of NBC with lipiodol, the use of large volumes of glue and the either too high or too low speed of injection [71].

Conclusions

The available data suggest that emergency endoscopic treatment with EVL combined with vasoactive agents and antibiotics given on suspicion of gastroesophageal bleeding, before the time of the initial diagnostic endoscopy, is the gold standard for the management of the AVB episode. Sclerotherapy may be used in situations where ligation is technically difficult. There are still areas on the management of variceal bleeding that should be further investigated. These are the use of tissue adhesives or fibrin glue in patients unresponsive to standard treatment, the best antibiotic prophylaxis, the use of anti-fibrinolytics, the treatment of gastric varices and the prognostic models determining timing of endoscopy, risk of aspiration pneumonia and risk stratification for prognosis.

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Chapter 13
TIPS: Primary Therapy or Rescue in Treatment of Acute Variceal Hemorrhage

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Introduction

The transjugular intrahepatic portosystemic shunt (TIPS) is a percutaneous imaging-guided procedure that diverts blood from the portal to the systemic circulation reducing portal pressure. Over the last 20 years the use of TIPS has evolved and become a standard treatment for some portal hypertension complications. Acute variceal bleeding (AVB) is one of the fields in which the TIPS strategy is becoming an important player, and its use has evolved from its use as a salvage treatment in the setting of uncontrolled AVB to more refined indications. TIPS is excellent at decompressing gastroesophageal varices and its insertion is very effective in controlling the AVB episode. However, TIPS deprives the liver of most, if not all, portal blood flow, increasing the risk of developing hepatic encephalopathy and progressive liver failure. For that reason, current attempts to optimize the use of TIPS are directed towards individualization for those populations of patients who are at high risk of failure from other treatments in which the high efficacy of TIPS may counteract its potential deleterious effects on liver function.

The Procedure

TIPS is usually executed under deep sedation or general anesthesia, and antibiotics against gram-positive commensal bacteria (third-generation cephalosporin) are highly recommended to prevent endotipsitis [1].

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The most standardized approach is to access the right internal jugular vein and catheterize the middle or hepatic right vein and nearby access the portal vein. Carbon dioxide wedged hepatic retrograde venography and real-time ultrasonography help to identify the portal vein localization and guide the transhepatic puncture facilitating the procedure [2].

Once the portal vein is catheterized, portal venous pressure gradient (PPG) is calculated through measurement of portal venous and inferior cava pressures. Subsequently, liver parenchyma is dilated using a balloon angioplasty catheter, and an expandable stent is placed and dilated until the target PPG of $\leq$12 mmHg is achieved. Deep sedation provokes respiratory pressure oscillation and underestimates PGG [3]; therefore, we recommend repeating PPG measurements after sedation recovery and readjusting stent diameter if necessary.

TIPS dysfunction is the main limitation of the procedure and can be due to thrombosis but mainly to pseudointimal hyperplasia growing inside the stent, causing a decrease in the diameter; however, this problem has been mostly overcome by using e-PTFE stents that have shown a reduced rate of TIPS dysfunction and of portal hypertension-related complications [4, 5]. Nevertheless, TIPS dysfunction, even using covered stents, is possible, and therefore TIPS patency should be checked through Doppler ultrasound every 6 months.

TIPS Use in Acute Variceal Hemorrhage

Esophageal Varices

Despite the implementation of intensive-care management and the use of combination treatment with vasoactive drugs, endoscopic therapy, and antibiotics, AVB mortality still reaches 15–20 % [6]. Moreover, even after the initial control of the bleeding episode, 30–40 % of the patients rebleed in the first 6 weeks. Variceal rebleeding peaks in the first 5 days, when 40 % of the rebleeding episodes occur; rebleeding risk slowly declines after week 4 [7]. Up to 10–20 % of patients present a refractory variceal bleeding, unresponsive to adequate pharmacologic and endoscopic therapy and require additional treatment. These patients can be stabilized with balloon tamponade, for a maximum of 24 h as a bridge therapy until definitive treatment can be performed. Decompression can be effectively achieved with derivative treatments, portosystemic surgical shunt, and TIPS [8]. The use of surgical shunt has substantially diminished, mainly due to the technical complex technique that requires very well trained surgeons; it currently represents an alternative for Child A and B patients when TIPS is unavailable [8]. e-PTFE stents are clearly the best alternative to control failure bleeding as they have reduced shunt dysfunction, clinical relapse, and need for re-intervention when compared with bare stents.

As a rescue therapy, TIPS placement achieves homeostasis in 95 % of the cases. However, despite controlling variceal bleeding, mortality in this setting is still very high, reaching 30–50 % of patients [9–12]. The long-term survival depends on the

severity of underlying liver disease and on the complications associated with the uncontrolled hemorrhage, especially renal failure and superimposed bacterial infections, rather than on the variceal bleeding per se. This poor outcome makes it mandatory to identify patients at very high risk of treatment failure and death with the aim to test whether applying alternative treatments may improve outcome.

Another rational option to improve outcome would be to place TIPS earlier, before uncontrolled bleeding occurs, in a subset of patients at high risk of rebleeding and death. Recent studies have focused on this issue, and identification of high-risk markers that enable the selection of a population requiring alternative or more aggressive treatments to prevent treatment failure may improve outcome.

A hepatic venous pressure gradient (HVPG) ≥20 mmHg measured during the acute variceal episode is able to identify patients with poor prognosis [13]. This criterion was used by Monescillo et al. to identify a high-risk population that benefits from TIPS placement within the first 24 h of the bleeding episode. Patients with an AVB and HVPG ≥20 mmHg treated with TIPS had a better survival and lower treatment failure than patients who did not receive the TIPS option [14]. However, this study shows several limitations; somatostatin plus sclerotherapy was considered as standard therapy, and the vasoactive drug was stopped right after endoscopy and non-covered stents were used [15]. These drawbacks together with the impossibility to perform HVPG measurement in numerous centers, especially in emergency situations, encouraged the performance of a subsequent multicenter European RCT [15]. In this study, clinical parameters that have been shown to accurately correlate with HVPG predicting the risk of treatment failure were selected [16–18] (Child C up to 13 points or Child B plus active bleeding at endoscopy) for identifying patients at high risk of treatment failure [15]. Once the AVB has been controlled, high-risk patients were randomized to receive an early TIPS, using e-PTFE covered stents, in the first 72 h, or the current standard of care (nonselective beta-blockers ± isosorbide mononitrate, endoscopic band ligation, and antibiotics). Despite the potential weakness of considering the Child Pugh during the acute bleeding period to select the population of the study, estimation of high risk was highly accurate. Patients treated with standard of care (drugs + EBL) presented a poor outcome (13 % had failure and 50 % rebleeding rate within 1 year), confirming a successful selection of high-risk patients. Early TIPS strategy as a primary therapy in those high-risk patients reduced failure to control AVB and rebleeding within 1 year to 3 %. Remarkably, mortality was significantly reduced in the early e-PTFE TIPS group where patients presented a 4 % 6 weeks and 33 % 1-year mortality, compared with 14 and 40 % in the drugs + EBL group.

Hepatic encephalopathy, one of the classic collateral harmful effects of bare stents, was not increased in the early TIPS group. Indeed, a trend towards a lower incidence was shown (28 % vs. 40 %), although more studies are needed to truthfully prove it. Other complications of cirrhosis such as ascites were less frequent in the early TIPS group; within 1 year 13 % patients developed ascites or had a worsening of previous ascites versus 33 % in the standard of care group. Additionally, hospitalization length and days in the ICU were also significantly lowered in the early TIPS group. It is important to remark that 7 of the 31 patients assigned to drug + EBL needed a TIPS as a rescue therapy; however, mortality in this setting

reached 57 % early after the rescue TIPS procedure, which confirmed the poor outcome even using TIPS in this situation and the benefit of placing a TIPS as early as possible in this high-risk situation.

A retrospective surveillance study from the same centers participating in the European RCT paper further supports the use of early TIPS in patients with the same original high-risk criteria [13]. In this study, a total of 75 patients with AVB and high risk of treatment failure were admitted since the publication of the original RCT. Thirty patients received the standard of care and 45 early e-PTFE TIPS. This study confirmed that the use of early TIPS reduces failure to control bleeding and rebleeding and improves survival in relation to the use of the standard of care. Preliminary data from France [19] and the UK [20], in two prospective small cohorts of patients with AVB and high risk using the same criteria as in the RCT, showed similar results. The first one [19] includes 23 patients and the second one [20] 31 patients who were all managed with the early TIPS strategy. Both groups reported similar excellent rates of rebleeding, survival, and EH (Table 13.1). Moreover, Rudler et al. [19] suggest that TIPS should be placed as early as possible, based on its better survival data in patients who receive a TIPS in the first 48 h in comparison to those who receive it after 48 but before 72 h.

All the available data strongly support the early use of TIPS using e-PTFE-covered stents in patients at high risk of treatment failure because this approach prevents failure to control bleeding, reduces rebleeding, and improves survival.

Nonetheless, the main challenge remains to recognize the more accurate prognostic factors in order to stratify patients according to their real risk. Child Pugh classification at the moment of AVB may be biased [21], as hemorrhage itself may deteriorate liver function, and albumin [22, 23] and coagulation values [24] may be altered. Also, 1-year mortality of Child B patients after a variceal bleeding may not highly differ from patients with and without active bleeding at first endoscopy [25], suggesting the need for a better definition of criteria that may select patients with high risk of rebleeding.

In agreement with this, MELD has been recently proposed [26] as an objective and excellent prognostic stratification of patients early after admission that could more efficiently select high-risk patients who might benefit from more aggressive treatments. Our group has recently described a MELD-based model to improve risk prediction in patients with cirrhosis and AVB that might be used to stratify patients for more individualized management.

Larger studies are needed to consolidate high risk and to strengthen the recommendation of the early TIPS in this population but also to identify new prognostic models that may help refine further the subgroup of patients who would benefit from an early TIPS strategy.

Gastric Varices

Management of bleeding from gastric varices has a different natural history than esophageal varices with a lower risk of bleeding but a worse outcome once hemorrhage occurs [27].

Table 13.1 Studies evaluating early TIPS in patients at high risk of failure

Study	N	High-risk criteria	Failure (%)	Rebleeding (%)	Hepatic encephalopathy (%)	Mortality (%)	Mean follow-up (months)
Monescillo et al. [14]	26	HVPG ≥20 mmHg	12	4	31	31	12
Garcia-Pagán et al. [15]	32	Child C Child B + active bleeding	3	0	25	12.5	14.6 ± 8.4
Garcia-Pagán et al. [13]	45	Child C Child B + active bleeding	2	4.4	51	13	13.1 ± 12
Rudler et al. [19]	23	Child C Child B + active bleeding	4.3	0	34	22	4.6 (1–4)
Britton et al. [20]	31	Child C Child B + active bleeding	N/A	9.7	16	19	20

TIPS has proven equal in the prevention of rebleeding from gastric and esophageal varices, controlling bleeding in more than 90 % cases [21, 28, 29].

TIPS has even shown superiority to cyanoacrylate injection in the prevention of rebleeding from gastric varices, although without survival benefit and a higher rate of encephalopathy [30]. To date, TIPS should be considered as a rescue treatment for those patients in whom glue injection fails to control bleeding.

Efforts focusing on a better selection of patients who may benefit from early TIPS may drive future research studies in this area. Risk stratification may lead to personalized medicine, improving AVB management and outcome.

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Chapter 14
How to Manage Gastric and Ectopic Varices?

Ashok Chaudhary and Shiv Kumar Sarin

Introduction

Portal hypertension is characterized by the presence of varices, the most common being esophageal varices. At the same time the presence of varices in stomach (gastric varices) and other sites (called ectopic varices) are other features of portal hypertension. Gastric varices (GV) are found in 20 % of patients with portal hypertension [1]. Ectopic varices (EcV) are dilated portosystemic collaterals located at unusual sites other than the gastroesophageal region; they constitute 1–5 % of all variceal bleeds in patients with intrahepatic portal hypertension, and 20–30 % of those with extrahepatic portal hypertension [2].

The hemodynamics of gastric varices differ from esophageal varices in that they do not correlate with HVPG, bleeding from GV is more severe with high mortality, and treatment is often challenging [3]. Varices developing at unusual sites, i.e., ectopic varices, are difficult to localize and manage because of their varied clinical presentations [4]. Hence, algorithms and stepwise management of these patients are needed.

Gastric Varices

Incidence and Prevalence

Gastric varices (GV) are found in 20 % of patients with portal hypertension [1]. The location of GV has important role in the management. The 2-year incidence of variceal bleeding from IGV1 and GOV2 type were higher (78 % and 54 %, respectively) than the lesser curve (GOV1) varices (28 %) [1]. IGV2 bleed only

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rarely (9 %) [1]. The overall rebleeding rate of gastric varices after complete variceal obliteration is variable and ranges from 10 to 42 % [5]. With the advancement in endoscopic technique and salvage therapy, the 6 weeks mortality from acute gastroesophageal variceal bleed has decreased from 40 % to approximately 15 % in recent years but mortality related to failure to control bleeding or early rebleeding (i.e., within the first 5 days after the initial bleeding episode) still remains high (up to 30–40 %) [6, 7].

Diagnosis

Gastric varices are diagnosed by endoscopy. Endoscopic ultrasound (EUS) is the test of choice for differentiation of GV from the gastric mucosal folds [8]. Alternatively, transabdominal ultrasound with Doppler, computed tomography (CT) scan with contrast, magnetic resonance angiography, portovenography, and interventional angiography can identify GV [9].

Classification

The most widely used classification system is Sarin's classification as shown in Fig. 14.1. This has been recommended for use by APASL, AASLD, and BAVENO guidelines and by expert panels because it is easy to use, has good correlation with

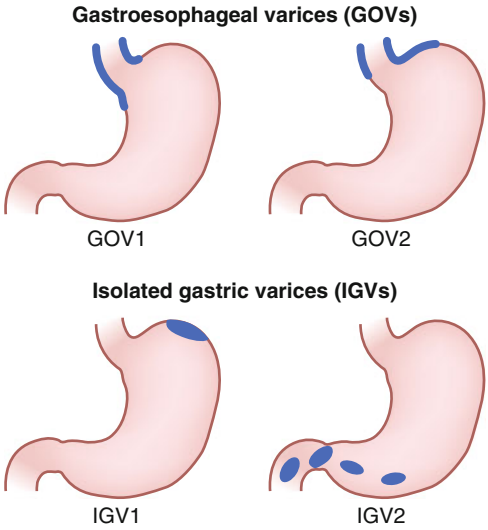

Fig. 14.1 Sarin's classification of gastric varices

Pathophysiology, and guides therapy [10–12]. This classifies GVs on the basis of their location in the stomach and their relationship with EVs.

Management

Primary Prophylaxis

Although primary prophylaxis has been studied and well established in managing esophageal varices, no guidelines are available for gastric varices. The hemodynamics of gastric varices differs from esophageal varices in that large gastric varices may develop at lower portal pressures due to the presence of gastrosystemic shunts. As gastric variceal bleed is more severe than bleeding from esophageal varices and associated with high mortality, primary prophylaxis should be considered for patients at high risk for bleeding (suggested to be those with an annual risk of ≥16 %) [13]. The therapeutic options include beta-blocker and/or cyanoacrylate glue. Data on primary prophylaxis for GV are very few. One recent RCT of primary prophylaxis by Mishra et al. [3] included 30 patients endoscopically treated with tissue adhesive, 27 patients treated with beta-blockers and 30 patients left untreated ($p = 0.003$). The overall bleeding rates were 10 % for patients treated with cyanoacrylate, 38 % for those on beta-blockers and 53 % for untreated patients. Overall mortality rates were 7 %, 17 %, and 26 %, respectively ($p = 0.113$).

Risk Factors for Gastric Variceal Hemorrhage include [3, 14–16]:

- Location of gastric varices (IGV1 > GOV2 > GOV1)
- Size of fundal varices (large > medium > small)
- Severity of liver failure (Child class C > B > A)
- Presence of red colour sign(RCS) over gastric varices
- Concomitant hepatocellular carcinoma
- Presence of portal hypertensive gastropathy
- MELD score ≥ 17

Thus, patients with high risk gastric varices should receive primary prophylaxis. Cyanoacrylate injection should be the first line of treatment for primary prophylaxis of “high risk” GV. Whether combined treatment with cyanoacrylate injection and beta-blockers has any added advantages over either of treatment given alone needs to be studied.

Acute Variceal Bleed

Incidence of bleeding from gastric varices is relatively low (10–36 %). The rebleeding rate after control of acute bleeding is high (34–89 %) depending upon the treatment modality and subsequent follow-up protocol [17].

Clinical presentations of variceal bleed are hematemesis and/or melena and are described as next:

- *Acute variceal bleed*: defined [10] as the bleed in a known or suspected case of portal hypertension, with the presence of hematemesis within 24 h of presentation, and/or ongoing melena, with last melanic stool within 24 h. The time of presentation is considered as *T*0 and any subsequent bout of hematemesis from *T*0 to 48 h of *T*0 will be considered as part of the same episode of acute variceal bleeding. Any bleeding occurring after 48 h will be considered as rebleeding.
- *Active bleeding*: It is defined [10] based upon endoscopic finding as the presence of spurting or oozing from the varix. It is a predictor of failure to control bleed and early rebleed.
- *Recent bleed*: Any clinically significant bleed occurring in the past 6 weeks of presentation [10].
- *Past bleed*: A clinically significant bleed occurring more than 6 weeks prior to presentation [10].

The amount of blood loss should be quantified based upon the history and clinical presentation as this indirectly decides the urgency of the situation, guides therapy, and predicts the outcome. The patient should be assessed for the amount of blood loss as per history (amount of loss, passage of clots, vomiting in emergency room) and clinical signs (hypotension, tachycardia, diaphoresis, and mental state).

A protocol-based stepwise approach for acute gastric variceal bleeding is the key for optimal outcome. We propose the following algorithmic approach:

- *Step 1—resuscitation*: It is the cornerstone to the success of endotherapy and survival. Initial resuscitative measures include protection of airway, breathing, and circulation.
  - *Airway protection*: Elective intubation prior to endotherapy should be done in patients with massive uncontrolled variceal bleeding, hepatic encephalopathy (grade III and IV), aspiration pneumonia, and in cases where there is difficulty in maintaining oxygen saturation above 90 % [10].
  - *Fluid replacement*: Colloids are preferred for volume resuscitation and crystalloids, particularly saline, should be avoided. The preferred maintenance fluid should be dextrose. The aim of volume replacement is to maintain systolic blood pressure around 90–100 mmHg, heart rate below 100 beats per minute, CVP 1–5 mmHg, diuresis of 40 mL/h.
  - *Blood volume*: Target hemoglobin level of around 8 g/dL and a hematocrit value of 24 %, depending on other factors, such as patient's comorbidities, age, hemodynamic status, and the presence of ongoing bleeding [12]. Packed red blood cells (PRBC) is the preferred blood component. The existing data in the literature demonstrate that correction of coagulation parameters and thrombocytopenia has no role in the management of acute variceal bleed. The use of recombinant activated factor VII (rFVIIa) in cirrhotic patients with acute variceal bleeding is not recommended. The promising role of thromboelastogram (TEG) in the peri-transplant period can be extrapolated for TEG-guided correction of coagulopathy.

- *Antibiotics*: Short-term antibiotic prophylaxis is mandatory as it reduces bacterial infections [18], variceal rebleeding, and death [19]. Quinolones and third-generation cephalosporins for a period of 5–7 days post-bleeding is recommended.
- *Vasoactive drugs*: The existing evidence for the use of vasoactive drugs in acute gastric variceal bleeding is limited. The efficacy of these drugs in controlling acute esophageal variceal bleed favors their use in the setting of acute GV bleed. RCTs comparing different pharmacological agents (vasopressin, somatostatin, terlipressin, and octreotide) have shown no differences regarding control of hemorrhage and early rebleeding, but vasopressin is associated with a higher incidence of adverse events [20]. The clinical efficacy of terlipressin versus placebo has been assessed in seven RCTs, and in a meta-analysis which showed that terlipressin significantly reduced the incidence of failure to control bleeding and mortality [21]. Terlipressin is the only pharmacologic agent that has been shown to reduce mortality (about 34 % reduction). Vasoactive drug treatment should be continued for 2–5 days.
- *Balloon tamponade*: Balloon tamponade is used as a bridge to definitive therapy. It is indicated in case of massive bleeding until endoscopy is done or after endoscopic therapy in case of failure to control bleeding until salvage treatment with TIPS/BRTO (transjugular intrahepatic portosystemic shunt/balloon-occluded retrograde transvenous obliteration) can be performed. Balloon tamponade is highly effective and hemostasis can be achieved in 80 % of cases, but has very high rebleeding rates if used as the sole therapy. Owing to its larger gastric balloon (600 mL), the Linton-Nachlas tube is more desirable for gastric variceal bleeding than the Sengstaken-Blakemore tube (200 mL). Careful placement is essential, especially in the sedated patient to reduce the risk of esophageal perforation from the inadvertent inflation of the gastric balloon in the esophagus.

- *Step 2—emergency endoscopy in AVB*: Diagnosis of acute gastric variceal bleeding is done by upper GI endoscopy. The endoscopic findings and definitions for management of acute gastric variceal bleed are shown in Table 14.1. Endoscopic therapy is the only established, initial, and often the definitive treatment for acute gastric variceal bleed. Presence of high blood flow in the GVs, underlying shunt leading to profuse bleeding and rapid deterioration despite aggressive resuscitation suggest rapid and urgent endoscopic therapy. Accordingly, once the patient becomes hemodynamically stable endoscopic treatment (EVL, glue, and thrombin) should be done as soon as possible: preferably the door-to-scope time should be less than 6 h as suggested by APASL guideline [10]. The choice of endoscopic therapy used often depends on local availability and expertise. It is advisable to use large channel (6 mm) therapeutic UGI endoscope to be able to do rapid suction and cleaning. The patient position is often important and several maneuvers, such as turning the patient to the right lateral decubitus, or placing the patient in a nearly sitting posture, are helpful to ensure a clean fundus, in order to be able to achieve good vision and proper injection or band placement.

Table 14.1 The definitions for management of acute gastric variceal bleed

Term	Definition
Suspected acute variceal bleed [16]	In a known or suspected case of PHT presence of hematemesis within last 24 h of presentation, and/or ongoing melena, with last melanic stool within last 24 h. The time frame for the acute variceal bleeding episode is 48 h. The acute variceal bleeding may be active or inactive at the time of presentation
Bleed from gastric varices [16]	On endoscopy, one of the following findings constitutes acute gastric variceal bleeding 1. Direct visualization of blood issuing from a gastric varix—spurting or oozing 2. Presence of a sign of recent bleed over a gastric varix—overlying clot or white nipple sign 3. Presence of gastric varices with red signs (risk factors for bleed) and the presence of blood in the stomach in the absence of another source of bleed/or stigmata of recent bleed on esophageal varices 4. Presence of gastric varices with red signs and clinical signs of upper GI bleed—melena or hematemesis—without blood in the stomach
Control of acute variceal bleeding [16]	1. Cessation of bleeding with hemodynamic stability for 24 h after therapy 2. In patients with active bleeding at endoscopy, cessation of bleeding should be confirmed at the end of the procedure
Failure to control acute variceal bleeding [23]	1. Failure to control acute bleeding after two attempts with the same endoscopic methods 2. More than one GV rebleeding episode 3. Bleeding to death 4. Change of modality
Rebleed from gastric varices [21]	New onset of hematemesis Coffee-ground vomitus Hematochezia Or melena With an increasing pulse rate over 100 beats/min And decreasing blood pressure below 90 mmHg after a 24-h period of stable vital signs and hemoglobin after endoscopic treatment
Early recurrence	Bleeding arising from the injected or nearby gastric varices within 48 h of endoscopic treatment
Late recurrence	Defined as bleeding arising from the injected or nearby gastric varices after 48 h after endoscopic treatment

– *Tissue adhesive/glue/cyanoacrylate/histoacryl*: Endoscopic variceal obliteration (EVO) is done by using tissue adhesives like *N*-butyl-2-cyanoacrylate and 2-octyl-cyanoacrylate, the former being used more commonly. The standard forward viewing endoscope is used, with its tip lubricated (acetone), using a disposable sclerotherapy needle primed with saline, sterile water, or dextrose. 1 mL aliquots of undiluted cyanoacrylate are injected. As the needle is withdrawn, a steady stream of water flush must be maintained. Initial hemostasis rates are up to 90 % in most series. Tissue adhesive injection is considered the endoscopic treatment of choice because of superior hemostasis rate

Table 14.2 Available randomized controlled trial studies of endoscopic treatment for gastric varices

References	Classification (GOV1/GOV2/IGV1)	Treatment modality	Hemostasis rate (%)	Rebleeding rate (%)	Follow-up
Sarin et al. [24]	0/8/28	GVS ($n=17$)	62	33	15.4 months
		GVO ($n=20$)			
Tan et al. [5]	53/25/19	GVL ($n=48$)	93	44	610 days
		GVO ($n=49$)	93	22	680 days
Lo et al. [23]	36/33/0	TIPS ($n=35$)	93	11	32 months
		GVO ($n=37$)		38	
Mishra et al. [26]	0/all GOV2 or IGV1	GVO ($n=33$)	N D	15	26 months
		Beta-blocker ($n=34$)		55	

and lower rebleeding rate, and is comparable to TIPS in achieving initial hemostasis as shown in Table 14.2. Complications are well known but rare, and include Thromboembolic phenomena (splenic, renal, pulmonary, cerebral, spinal, and coronary), sticking of the needle in the varix, gastric ulceration, retro-gastric abscess, visceral fistula formation, bacteremia/sepsis, and rarely death. Embolic and thrombotic phenomena are associated with larger volume of glue injection and it is recommended not to exceed 2 mL per session [22]. However, higher volumes could be injected (2 mL/column) if more than one columns are to be injected. Repeat sessions should be performed after about 4 weeks, until endoscopic obliteration is achieved. The obturation of the varices is assessed by blunt palpation using the hub of the same injector with the needle retracted. EUS is useful to identify residual flow [8]. Rebleeding rates after cyanoacrylate injection vary from 7 to 65 % (with most of the larger series reporting rates below 15 %) and is often seen in patients with associated portal vein thrombosis (Table 14.2) [5, 23–26].

– *Thrombin*: Thrombin is a locally acting hemostatic agent that converts fibrinogen to a fibrin clot and also helps in platelet aggregation. It is available as a sterile, lyophilized powder, pooled from human plasma donors. After reconstitution, it is injected through a disposable sclerotherapy needle with a standard gastroscope in aliquots of 1 mL (each mL = 250 U) and hemostasis occurs within 60 s. The average dose of injected thrombin is somewhere between 1,500 and 2,000 U [17]. The results of the use of thrombin in different studies are shown in Table 14.3 [27–32].

  Thrombin injection is highly effective with initial hemostasis rates >90 % and rebleeding rates varying from 0 to 50 %. Procedure and injection-related side effects are infrequent. The drawbacks of thrombin are the cost, anaphylactic reaction (presently uncommon since human preparations have replaced the previously used bovine preparations), and risk of transmission of viruses.

– *Endoscopic sclerotherapy*: Endoscopic use of sclerosants (ethanolamine oleate or polidocanol) similarly to what is done for esophageal varices is another option. During acute GV bleeding, EVS (endoscopic variceal sclerotherapy)

Table 14.3 Use of thrombin in different studies

References	No. of patients	GV type	Primary hemostasis (%)	Rebleed (%)	Mortality (%)	Follow-up
Williams et al. [27]	11 Cirrhosis $n=10$ PVT $n=1$	Cardia $n=2$ Fundus $n=9$	100	27	0	9 months
Przemioslo et al. [28]	52 Cirrhosis $n=49$ Cirrhosis with PVT-3	GOV1 ($n=31$) GOV2 ($n=21$)	94	16	8	15 months
Yang et al. [29]	12 Cirrhosis $n=9$ PVT $n=1$ Hepatic metastasis ($n=1$)	GOV1 ($n=1$) GOV2 ($n=10$) Not reported ($n=1$)	100	25	17	17 months
Heneghan et al. [30]	10 (cirrhosis $n=10$)	GOV1 ($n=4$) GOV2 ($n=6$)	70	50	50	8 months
Datta et al. [31]	15 (cirrhosis $n=12$) PVT ($n=3$)	GOV1 ($n=11$) GOV2 ($n=2$) IGV1 ($n=2$)	93	28	7	1 month
Ramesh et al. [32]	13 cirrhosis ($n=13$)	GOV ($n=12$) IGV ($n=1$)	93	0	Not reported	22 months

achieves immediate control of bleeding in 60–100 % of cases but is associated with unacceptably high rebleeding rates of up to 90 % [33]. EVS achieves variceal eradication in 40–70 % of all GV patients treated electively [34], but according to Sarin et al. [33] the success rate is dependent upon the location of varices: eradication rates of 95 % can be achieved with GOV1, but the technique is less effective for GOV2 and IGV1. Multiple studies including RCTs showed that EVS is less effective in the treatment of GV than of EV, probably due to the high-volume blood flow through the GV compared with the EV. This may result in rapid flushing away of the sclerosant in the bloodstream, which may require large amounts of sclerosant, leading to a higher rate of side effects, such as retrosternal and abdominal pain, and fever [1]. Rebleeding after elective EVS was <20 % with GOV1 and GOV2 but high in patients with IGV1 (53 %). Most bleeds were due to ulcers at the injection site [1].

To summarize: EVS is effective and appropriate for acute GOV1 bleeding but is less effective for fundal varices (GOV2 or IGV1), as a consequence, the use of cyanoacrylate glue is the first choice if available, and EVS should be considered as an alternative.

– *Variceal band and loop ligation*: Endoscopic variceal ligation is the gold standard endoscopic therapy for esophageal varices but is less effective for gastric varices due to: (1) thick mucosa overlying the varices, with difficulty in suction during band ligation; (2) larger size of varices which causes difficulties in sucking the varices in the suction hood of the banding device; (3) development of post-EVL ulcer bleeding which may be fatal because of the underlying hemodynamic alterations; (4) the overall higher rebleeding and recurrence rates of varices (lesser degree of deep fibrosis of the varices) [35].

  EVL with nylon or stainless steel snares or standard rubber bands has been used. GV smaller than 2 cm in diameter can be ligated with standard rubber bands, whereas larger diameter GV requires the use of larger detachable snares [36].

  Only one RCT by Lo et al. [23] compared the use of EVL using rubber bands against EVO and showed that EVL was less effective than EVO in controlling acute GV bleeding (45 % vs. 87 %) and had a higher rebleeding rate (54 % vs. 31 %). The eradication rates of EVL and EVO were comparable (45 % vs. 51 %).

– *Role of EUS*: EUS along with color Doppler has been shown to be more sensitive than conventional endoscopy for detecting gastric varices. Iwase et al. [37] showed that linear Doppler EUS easily detects the persistence of blood flow in gastric varices after cyanoacrylate therapy and suggests a higher risk for recurrent bleeding. An interesting study by Lee et al. [8], in patients with acute GV bleeding compared "on-demand" cyanoacrylate injection for recurrent bleeding ($n=47$) with scheduled biweekly EUS-guided glue injection till obliteration of all residual varices ($n=54$). The study showed that repeated sessions on a scheduled basis significantly reduced the risk of late rebleeding compared with the on-demand approach (19 % vs. 45 %). In a prospective case series [38] of 5 patients with bleeding gastric varices, EUS-guided

injection of cyanoacrylate directed at the perforating veins achieved hemostasis in all patients, with no cases of recurrent bleeding over a 10-month follow-up. Variceal eradication was successful in 2 patients after 1 session and in 3 patients after 2 sessions (mean 1.6).

In another study using a novel approach, transesophageal EUS-guided coil embolization and cyanoacrylate injection [39] of gastric fundal varices reduced the amount of glue and the number of sessions needed for complete EVO, with control of acute bleeding in all cases. Among 24 patients with a mean follow-up of 193 days (range 24–589 days), gastric fundal varices were obliterated after a single treatment session in 23 (96 %) and no rebleeding was attributed to GV. There were no procedure-related complications and no symptoms or signs of CYA glue embolization.

Thus EUS is an important tool and its use is expanding in the management. It easily: (1) localizes GV; (2) differentiates GV from other bleeding mucosal lesions; (3) detects perforating veins; (4) can guide the injection of sclerosants, glue or thrombin, dictating both the amount and the site when adequate visualization by conventional endoscopy is not possible due to active ongoing bleeding; (5) can detect, during follow-up, residual varices, perforating veins, and collaterals to guide further sessions of endoscopic therapy and may decrease the risk of rebleeding.

- *Step 3—salvage radiologic therapies*: After failure to control bleeding during endoscopy salvage, rescue radiologic interventions are the next option. As per the APASL guideline [10], second look endoscopy should be performed after initial failure to control bleeding or early rebleeding and balloon tamponade should be used as a bridge until definitive therapy is started.

  Salvage radiologic approaches include TIPS, BRTO, BO-EIS (balloon-occluded endoscopic injection sclerotherapy), and BATO (balloon-occluded antegrade transvenous obliteration).

  – *TIPS*: The principle behind the use of TIPS is the reduction of portal pressure by creating a portosystemic bypass. TIPS is indicated in two situations, i.e., (1) in acute variceal bleeding as a rescue therapy and (2) to prevent recurrent bleeding after initial endoscopic therapy. See Fig. 14.2a–g.

    Patients presenting with acute gastric variceal bleeding may have HVPG <12 mmHg (which is defined as the lower limit for variceal bleeding/clinically significant portal hypertension for esophageal varices) in the majority of cases. In patients with pre-TIPS HVPG of <12 mmHg, the decrease in gradient after TIPS does not affect the risk for rebleeding, whereas it has been shown that in patients with pre-TIPS HVPG >12 mmHg the risk for rebleeding is significantly reduced [8]. Sanyal et al. [40] showed that patients undergoing TIPS for gastric variceal bleeding had a spontaneous gastro-renal shunt (GRS) in 67 % of cases (4 of 6 patients) and in half of the patients (6 of 12) the varices failed to resolve. Ryan et al. [35] found that in 2 patients with large GV associated with a spontaneous GRS, having pre-TIPS HVPG < 12 mmHg, the post-TIPS gradient was marginally reduced (only by 1 mmHg) and TIPS had no effect on blood flow through the GV in this group of patients.

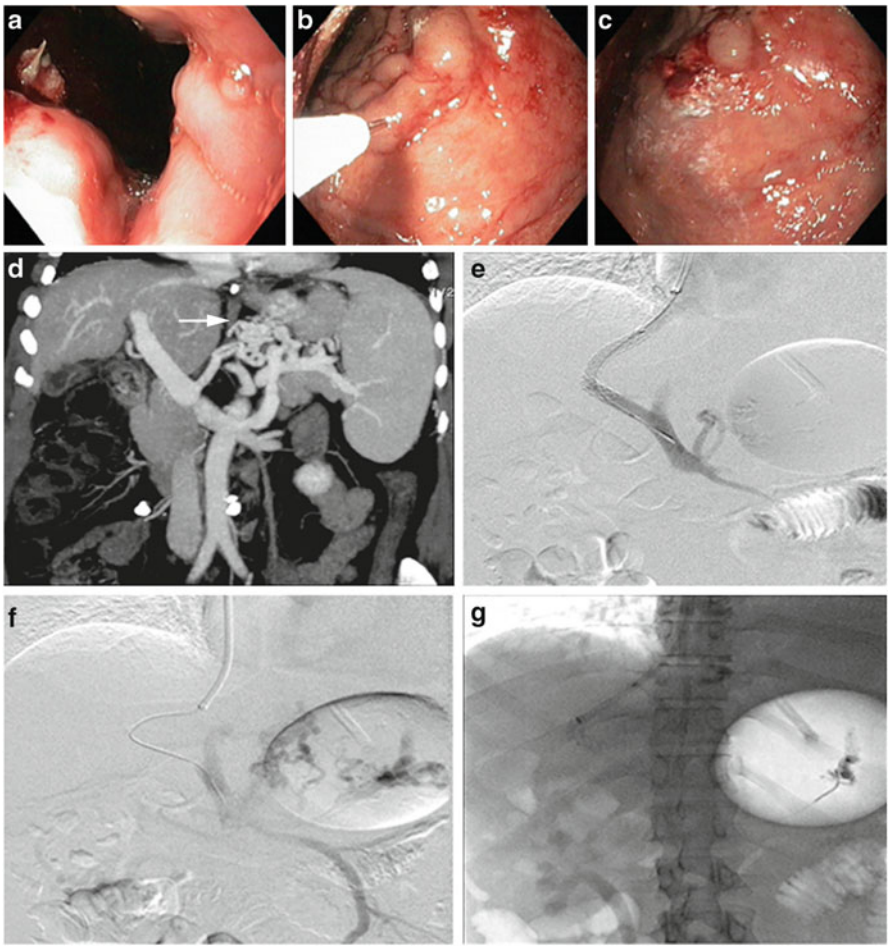

Fig. 14.2 (**a**–**g**) A 40-year-old male with alcoholic cirrhosis presented with acute variceal hemorrhage. Urgent endoscopy revealed small esophageal varices with active bleeding from GOV2. Glue was injected and hemostatis was achieved but the patient again rebled within 48 h of admission. Abdominal CT scan revealed large (**a**, **b**, **c**) paraesophageal and gastric varices (*arrow* in (**d**)). The patient underwent a TIPS procedure (**e**). Portal venography post stent placement demonstrated persistent filling of the large gastric varices (*arrow* in (**f**)) despite adequate reduction in the portal pressure. These varices were successfully embolized with glue (*arrow* in (**g**))

Thus, the efficacy of TIPS in preventing GV rebleeding in a subgroup of patients with low HPVG and GRS needs further studies [26].

Control of acute GV bleeding with TIPS can be achieved in up to 95 % of patients and is comparable to cyanoacrylate and thrombin [35]. On follow-up the 1-year rebleeding rate is between 10 and 30 %, the incidence of new-onset encephalopathy is 3–18 %, and the overall 1-year survival varies between 58 and 80 %, which mainly depend upon the severity of the underlying liver

disease. The technical success rate of TIPS is up to 100 % in most of the series and some studies suggested that covered stents might have a survival advantage and possibly lower encephalopathy over bare stents.

Studies have shown that bare stent dysfunction occurs in 30–80 and 47–90 % of patients by 1 and 2 years post-TIPS, respectively [4]. Doppler ultrasound is 70 % sensitive and 90 % specific in predicting stent dysfunction and surveillance at 6 months intervals with this technique is adequate. Some centers suggested to perform portal angiography for surveillance every 6 months as this technique is highly sensitive and allows concomitant therapeutic intervention if necessary [35].

Thus to summarize TIPS has an important role in the management of bleeding gastric varices as a rescue therapy, but in places where cyanoacrylate is readily available, it should probably be used after failed endoscopic therapy. Appropriate patient selection as well as severity of the underlying liver disease is critical, and cost-effectiveness of the procedure along with availability of TIPS in a resource poor setting should be taken into consideration.

– *Balloon-occluded retrograde transvenous obliteration*: BRTO is a vascular interventional technique performed in patients with a GRS, in which a balloon catheter is advanced from a transfemoral (systemic venous) approach and positioned and inflated to occlude the GRS near its base at the left renal vein. After balloon occlusion, sclerosant is injected; stagnation of the sclerosant within the shunt and in the gastric varices leads to the obliteration of the varices. Preprocedural imaging is important to ascertain the presence and diameter of the shunt, so that a balloon whose diameter will match the diameter of the shunt can be selected [41].

  BRTO is feasible only in patients with a known GRS (which is present in 85 % of patients with GV). In a study of acute bleeding, hemostasis was achieved by BRTO in 100 % (16/16) of patients and the rebleeding rate was 0 % during almost 2 years of follow-up, with a high eradication rate. The most common complications reported are hemoglobinuria, abdominal pain, transient fever, pleural effusion, transient worsening of liver biochemistry, shock, and atrial fibrillation. Long-term complications are worsening of EV in up to 50 % of patient, the appearance of ectopic intestinal varices or rectal varices and extension of thrombus to the portal vein and renal vein. Chikamori et al. [42] showed that the incidence of worsening of esophageal varices was significantly reduced when BRTO was preceded by partial splenic embolization (PSE) (9 % vs. 45 %), without any differences in gastric variceal disappearance rates or survival. See Fig. 14.3a–d.

  In patients with GV bleeding and uncontrolled ascites and/or hepatic hydrothorax, or high-risk esophageal varices, consideration of TIPS with BRTO is advisable to simultaneously achieve portal decompression [41].

– *Balloon-occluded endoscopic injection sclerotherapy*: This is another approach which does not require a GRS. The portal vein is cannulated by a transhepatic route and the GRS (if present) is cannulated via the transfemural route through the left renal vein. Through the portal vein, the smaller veins

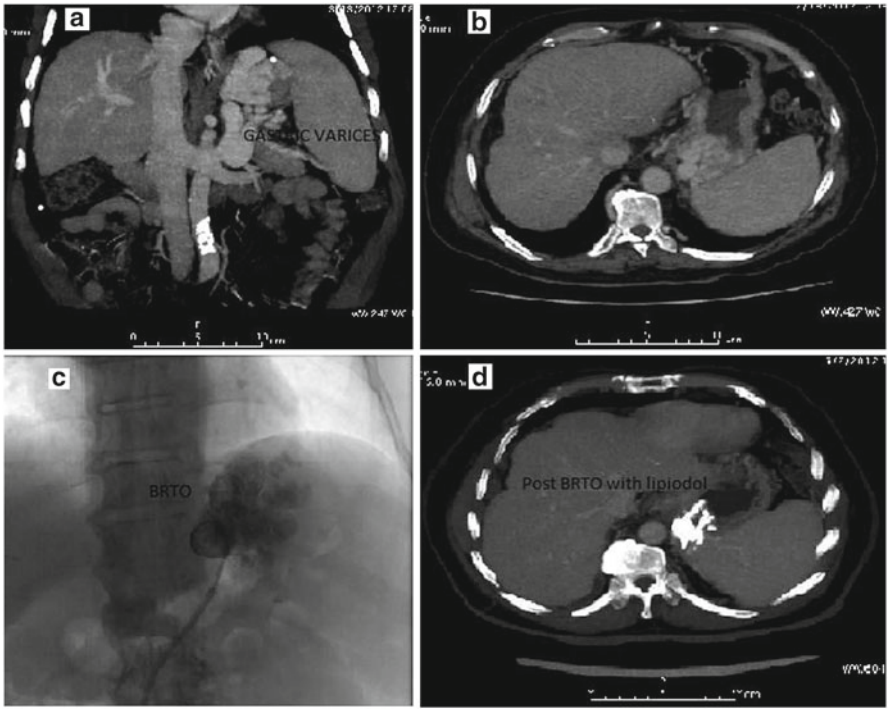

Fig. 14.3 (**a**–**d**) A case of gastric variceal bleed had undergone BRTO. The *upper panels* (**a**, **b**) show preprocedure CT with gastric varices and gastro-renal shunt. (**c**, **d**) Show BRTO intraprocedure image and 3 month post-BRTO follow-up CT with residual varices and lipiodol

supplying the varices are occluded with coils and the main supplying vein is also occluded with a balloon. The varices are then injected with sclerosant endoscopically. After treatment, the catheters remain in situ for 24 h to permit maximal sclerosis of the varices. This is a potentially effective means of eradicating GV, it seems similar to BRTO in terms of safety and efficacy, and has some added advantage in that it can be performed in patients without GRS [35].

– *Balloon-occluded antegrade transvenous obliteration*: BATO in which a balloon catheter is advanced from a transhepatic (portal venous) approach and positioned and inflated in the left gastric vein (LGV) or coronary vein near its origin at the main portal vein (PV). PTE (percutaneous transhepatic embolization), trans-TIPS BATO are used in the absence of GRS or when technical difficulty arises in approaching the variceal columns [41].

The details of the available studies on BRTO used for GV bleeding are shown in Table 14.4 [42–49].

In conclusion, BRTO is a very effective form of treatment for gastric varices in patients with large gastrosystemic shunts in whom there is failure to control acute gastric variceal bleed; who are poor candidates for TIPS, such as patients with a thrombosed portal vein, hepatic encephalopathy, or a low

Table 14.4 The detail of the available studies on BRTO used for GV bleeding

References	Study type	Treatment	No. of patients	Type of GV	Variceal disappearance	Rebleeding	Esophageal varices worsening	Mean follow-up
Kanagawa et al. [43]	Case series	BRTO	32	Fundal	97	0	–	14
Kitamoto et al. [44]	Case series	BRTO	23	Fundal (11 active bleeder)	83	9	35	21
Fukuda et al. [45]	Retrospective	BRTO	43	Fundal	79	NR	17	30
Ninoi et al. [46]	Retrospective	BRTO	78	Fundal (83 %) Cardiac (17 %)	97	1.5	66	23
Cho et al. [47]	Retrospective	BRTO	41	Fundal (47 %) Cardiac (29 %) Rest both	80	0	67	21
Chikamori et al. [42]	Retrospective comparative	BRTO/BRTO+PSE	14/19	GOV-21 % IGV-79 %	100/100	0	45/9	–
Akahoshi et al. [49]	Case series	BRTO	68	GOV2-46 % IGV1-54 %	97	3	17	66
Hong CH et al. [48]	Retrospective comparative	BRTO/Glue	13/14		–	71/15	–	17

Table 14.5 Surgical therapies for acute GV bleeding and on follow-up

Surgery		Rebleeding rate	Complications
Shunt surgery	Total shunt (side to side, end to side)	Excellent control of bleeding	Very high HE
	Partial shunt (side to side calibrated shunt)	Less	Low HE
	Selective shunt (DSRS)	<10 %	Low HE
Non-shunt surgery	Transection		
	Devascularization	>40 %	
Splenectomy	For left-sided PHT isolated splenic vein thrombosis	Curative	
Hassab's operation [50–53]	Devascularization of the upper stomach with splenectomy.	Can be performed in advanced cirrhosis No surgical expertise required Laparoscopic approach feasible	
Liver transplantation	Corrects the disease	Nil	As for LT

HVPG; who have large high risk gastric varices for secondary prophylaxis after initial endoscopic therapy.

- *Step 4—surgical therapies*: Surgery is currently considered only as salvage therapy when endoscopic, medical, and radiologic therapies fail in patients with Child-Turcotte-Pugh class A cirrhosis or in patients who live at a great distance from centers that can manage variceal bleeding adequately [6]. Surgical therapies for acute GV bleeding are shown in Table 14.5.

  With rapidly evolving technology, advances in endoscopic approach and use of EUS to assess the vascular anatomy and EUS-guided GVO, and the availability of salvage radiological procedures such BRTO and TIPS, surgery is falling out of favor. Etiology of portal hypertension, severity of liver disease, response to prior treatment, and the possibility of future liver transplantation must be considered while considering surgical management. Hassab's operation is a useful technique in which devascularization of the upper stomach along with splenectomy is performed and can be effective in acute gastric variceal bleeding with poor liver function [50–53].

Secondary Prophylaxis

Medical Therapies

There is little evidence for the use of drugs for secondary prevention. Few studies have shown the efficacy of drug therapy for the prevention of GV rebleeding after successful endoscopic variceal obturation [54]. In a study by Mishra et al. [26] the GV rebleeding rate in the cyanoacrylate group was significantly lower than in the

beta-blocker group (15 % vs. 55 %, $p = 0.004$) and the mortality rate was lower (3 % vs. 25 %, $p = 0.026$) during a median follow-up of 26 months. The median baseline and follow-up HVPG in the cyanoacrylate group were 15 (10–23) and 17 (11–24) mmHg ($p = 0.001$) and for the beta-blocker group 14 (11–24) and 13 (8–25) mmHg ($p = 0.003$).

Thus, drug therapy with beta-blocker should be continued: (1) if it is well tolerated; (2) in the presence of concomitant esophageal varices or of a documented HVPG greater than 12 mmHg as an adjunct to endoscopic therapy.

Endoscopic Therapies

After the index bleeding, secondary prophylaxis with endoscopic therapy is better than drug therapy and the use of tissue adhesive is the modality of choice. To conclude, repeated tissue adhesive injection until obliteration of GV with or without beta-blocker is the ideal secondary prophylaxis. In resource poor setting, due to unavailability of facilities or lack of expertise for glue injection, GV sclerotherapy or band ligation may be considered, keeping in mind the high risk of rebleeding.

Interventional Radiologic Approach

There are clear recommendations for the routine use of these techniques for secondary prophylaxis of GV bleeding. The options include TIPS, BRTO, and BO-EIS. All these modalities achieve good control of acute bleeding as well as very minimal rebleeding. The preferences for such therapies include (1) TIPS to be considered in cases with HVPG > 12; (2) BRTO for cases with low portal pressure (HVPG < 12 mmHg), presence of PVT, or large GRS; and (3) BO-EIS when it is difficult to perform BRTO [41].

Partial Splenic Embolization

Splenectomy or PSE per se or prior to BRTO has been considered as a modality for GV bleeding, to prevent rapid progression of esophageal varices. The procedure involves super-selective catheterization and embolization of the intrasplenic arterial branches, usually with polyvinyl alcohol particles. PSE leads to reduction of portal venous pressure, reduction in splenic size with improvement of the hypersplenism-induced thrombocytopenia, enhanced hepatic function, and reduced encephalopathy [17]. As far as secondary prophylaxis against GV rebleeding is concerned, patients have been followed in four case series showing an 80 % reduction in bleeding rates with follow-up times ranging from 3 to 50 months. Post-embolization syndrome is almost universal with abdominal pain, fever, nausea, and anorexia.

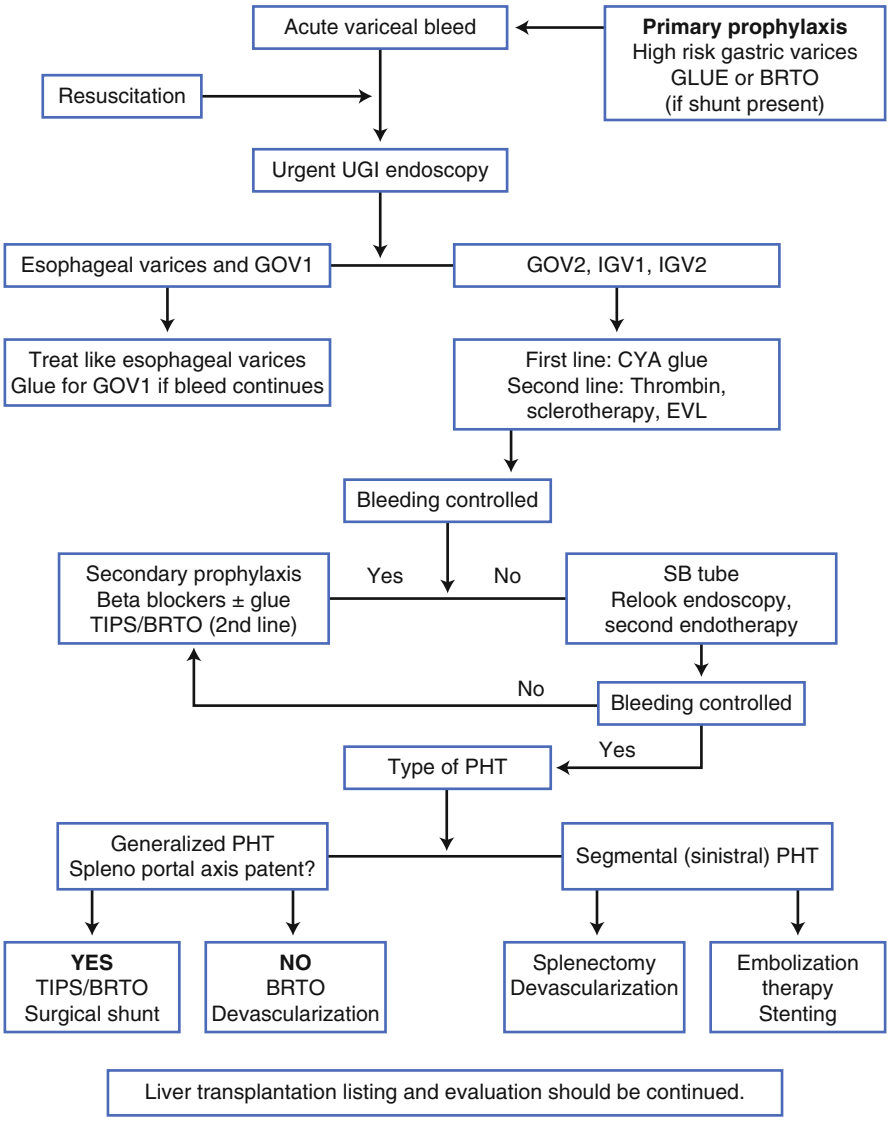

Fig. 14.4 Algorithm for GV bleed management

Overall, the literature is limited in quality, but, given the potential benefits of PSE, further investigation is warranted to allow evidence-based evaluation of its use in the treatment of GV.

An algorithmic approach to gastric variceal bleed is shown in Fig. 14.4.

Conclusions

Gastric variceal bleeding is associated with high morbidity and mortality rates. Early detection and control of bleeding are important. The patient should be started with vasoactive drugs (door to needle time within 30 min) and early endoscopy after initial hemodynamic stabilization (door to scope time <6 h) is recommended. Endoscopic variceal obturation by glue is the method of choice followed by repeated session every 4 weeks until complete obliteration of varices. Rescue therapies include TIPS or BRTO. Surgery has a limited role for selected subgroups. Secondary prophylaxis with beta-blocker and endoscopic therapy is ideal.

Ectopic Varices

Incidence and Prevalence

EcV are dilated portosystemic collateral veins located in sites other than the gastroesophageal region [4]. They constitute 1–5 % of all variceal bleeds in patients with intrahepatic portal hypertension and 20–30 % of those with extrahepatic portal hypertension [2]. EcV are rare and are a challenge to the clinician because of the difficulty in their management and the high mortality secondary to their initial bleeding (up to 40 %) [26, 40].

Site of Distribution

EcV are defined on the basis of their location (Table 14.6). They can occur in the stomach (isolated gastric varices—IGV2 of Sarin's classification), the duodenum, jejunum, ileum, colon, rectum, at peristomal sites, in the biliary tree, peritoneum, umbilicus, falciform ligament, bare area of the liver, splenic ligament, urinary bladder, right diaphragm, ovary, vagina, and testis. The distribution of varices is difficult to quantify due to difficulty in their diagnosis and unusual location. Data regarding the incidence and/or severity of bleeding in each site are not currently available and only center-based case series were available. The duodenum is the most common site (17–40 %) [55–57]; other relatively common locations are the small intestine (4–18 %) [58–60], the colon (3.5–14 %) [57–61], the rectum (8–40 %) [62], the peritoneum (9 %) [57], and peristomal areas (5.8 %) [58]. The other rare sites are vagina, ovary, and gall bladder. Familial cases of EcV have also been reported [63]. See Fig. 14.5.

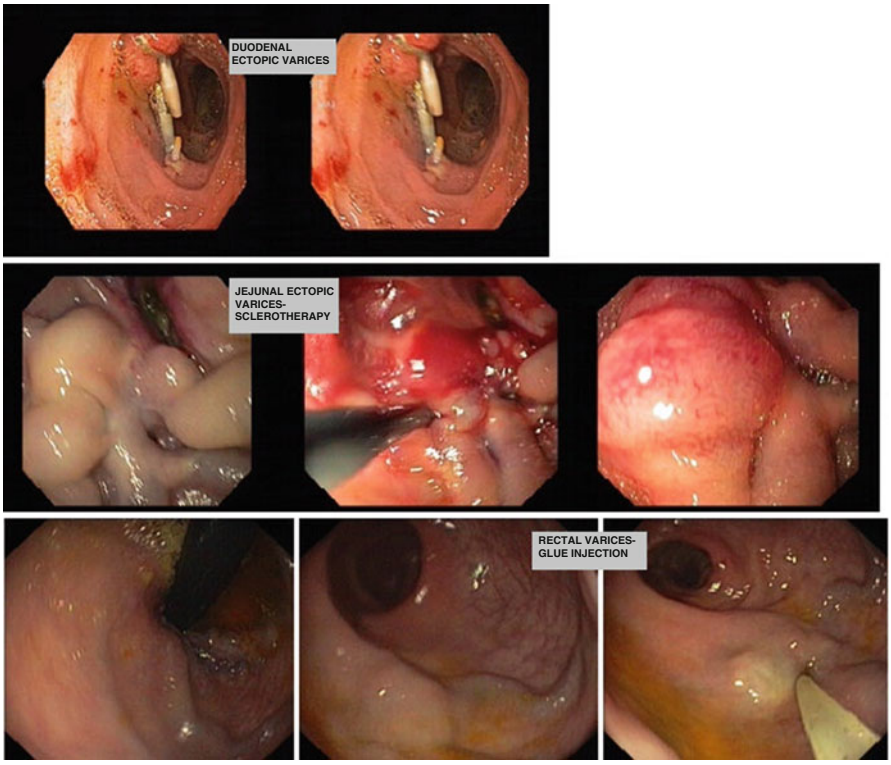

Fig. 14.5 *Top row*: Duodenal ectopic varices in a patient of EHPVO with portal biliopathy. The sent in CBD is visible. *Middle row*: Jejunal duplication cyst with jejuna ectopic varices at the ostia presenting with recurrent bleed, underwent balloon enteroscopy and sclerotherapy. *Bottom row*: A cirrhotic with recurrent lower GI bleed from rectal varices, underwent glue injection for the same

Classification

A classification was proposed by us depending upon the location of varices and is shown in Table 14.6.

Management

Clinical Presentation

The majority of EcV are detected during routine endoscopy or colonoscopy or during angiography performed for some other reason in asymptomatic patients. The clinical presentation of EcV is variable and reported in Table 14.7 [4].

Table 14.6 Proposed classification depending upon the location of ectopic varices

Luminal	Extra luminal
Isolated gastric varices	Intraperitoneal
Duodenum	Retroperitoneal
Jejunum	Umbilicus
Ileum	Around the falciform ligament
Colonic	Gallbladder and biliary tree
Rectal and anal canal	Perisplenic
Peristomal	Right diaphragm
	Ovary
	Vagina

Table 14.7 Clinical presentation of ectopic varices

Overt obscure GI bleed
Occult GI bleed
Incidentally detected
Iron-deficiency anemia
Mucocutaneous bleeding from the stomal site
Hematemesis
Hematochezia
Intra-abdominal bleed (hemoperitoneum)
Hypovolemic shock
Hemorrhagic pleural effusion
At autopsy

When to Suspect Ectopic Variceal Bleed?

Presentation with hematemesis or hematochezia is the most common. EcV bleeding should also be suspected when a patient with portal hypertension shows a sudden fall in Hb >2 g, tachycardia, sweating or hemodynamic instability, abdominal pain, increase in abdominal girth, rising lactate, and no obvious source of bleeding is identified [2, 4]. Small intestinal ectopic variceal bleed should be suspected when patients present with a triad of portal hypertension, hematochezia without hematemesis, and previous history of abdominal surgery [64].

Diagnosis of Ectopic Varices

The diagnosis depends upon the location of ectopic varices. Luminal EcV are often diagnosed by endoscopy.

Endoscopy remains the best method of diagnosing IGV2, duodenal varices as well as rectal varices. Lower GI bleeding should be attributed to rectal varices based on three criteria: rectal varices and the presence of fresh blood in the rectum, sigmoid colon free of fresh blood, and the absence of hemorrhoids or colopathy. At ileocolonoscopy, 18 % of patients with liver cirrhosis and/or portal hypertension have ileal varices [61]. *Double Balloon Enteroscopy* (*DBE*) can visualize the whole

small bowel and perform necessary endoscopic interventions [64, 65], thus DBE has both diagnostic and therapeutic potential.

In one study [65], *video capsule endoscopy* (*VCE*) demonstrated small intestinal varices in 8.1 % of patients with portal hypertension. VCE has no procedure-related side effects and is noninvasive, it can detect small varices that are not seen at endoscopy, and the overall concordance between endoscopy and VCE was 96.9 and 90.6 % for the diagnosis of varices and gastropathy, respectively [66]. However, DBE was considered better than capsule endoscopy due to added therapeutic capability.

EUS has been found to be superior to endoscopy to diagnose rectal varices [37]. EUS can be used to better localize and differentiate EcV from other bleeding mucosal lesions [67, 68].

Computed tomography (*CT*) *and angiography* can detect bleeding duodenal varices if they are massive [69]. Angiographic evaluation of EcV can be performed either by direct visualization of the venous system through transhepatic portography or by indirect visualization of the venous phase after splenic and/or mesenteric arteriography. It provides information about splenic vein patency. Transhepatic portal venography has been used to confirm EcV by finding abnormal splanchnic vessels feeding from either the superior or the inferior mesenteric vein [70].

Percutaneous Doppler ultrasound can detect peristomal collaterals and may be used to guide variceal sclerotherapy. Choi et al. [71] have described the use of multislice helical CT to detect stomal varices.

Other modalities include Technetium-99 m red blood cell scintigraphy, CT angiography, CT enteroclysis, and laparotomy [2].

The algorithmic approach to diagnose EcV is shown in Fig. 14.6.

Stepwise Approach in Management of Ectopic Variceal Bleeding

As there is no established guideline, and the management is center-specific, based on experience and expert opinion and mostly extrapolated from the existing guidelines for acute variceal bleeding management. Here we suggest a stepwise approach to such cases as outlined next.

- *Step 1—initial management*: The initial step for management includes general supportive measures, i.e., appropriate resuscitation with crystalloid or other blood products, according to the APASL guidelines, the goals are to maintain systolic blood pressure at least at 90–100 mmHg, and the heart rate below 100 beats/min, with a hemoglobin level around 7–8 g/dL (hematocrit of 21–24). Prophylactic antibiotics should be given.

  Pharmacotherapy with vasoactive drugs should be initiated as soon as the diagnosis of EcV bleed is made or suspected. Somatostatin or its analogue octreotide may be beneficial and should be continued for 3–5 days after confirmation of the diagnosis [72]. Octreotide has been shown to be effective in the control of bleeding colonic varices [73]. Terlipressin use should be considered but no definite recommendation for the dose or frequency of administration is available at present.

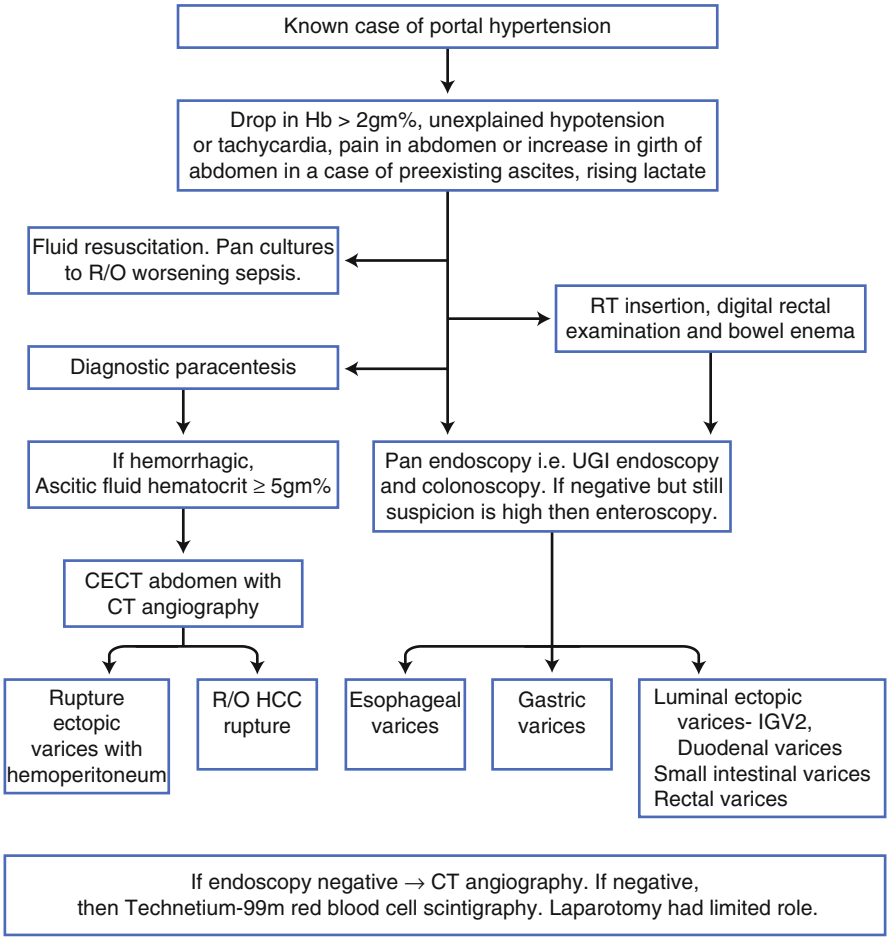

Fig. 14.6 Algorithm for ectopic variceal bleed management

- *Step 2—endoscopic interventions*: Once the patient is hemodynamically stable, emergency upper GI endoscopy should be performed. The door to scope time should be less than 6 h [10]. If endoscopy fails to show the source of GI bleeding, colonoscopy after a rapid preparation with polyethylene glycol solution delivered via a nasogastric tube should be the second step of investigation. In areas beyond the reach of conventional endoscopic procedures, enteroscopy can be performed electively [10].

  The endoscopic stigmata for bleeding EcV include—finding a spurting vessel, signs of recent bleed such as a "white nipple" or an adherent clot (Level of evidence 3b, Grade C) [10] and endoscopic management with band ligation [74, 75] or endoscopic sclerotherapy [76, 77] or glue injection should be done as discussed in detail next. The various endoscopic approaches include:

- *Injection sclerotherapy*: The endoscopic injection of ethanolamine oleate, bucrylate [78–80], and thrombin [81, 82] is being used with variable success rate for bleeding varices in the duodenum [77, 83] and small bowel and also for controlling the bleeding from peristomal varices with no injury to the stoma from the sclerosant [83]. Cyanoacrylate and thrombin are promising in the management of gastric and EcV with high hemostasis and low rebleeding rates [84]. The risks associated with cyanoacrylate include endoscope damage, and thromboembolic complications [84] but the use of thrombin as an alternative is technically easy to administer without major complications [32]. However, there have been no randomized trials to directly compare the efficacy of thrombin vs. cyanoacrylate.
- *Band ligation*: Although EVL is the treatment of choice for esophageal varices, this treatment [67, 75, 85, 86] is successful in halting bleeding but of limited use when the EcV are larger than 15 mm. EVL does not obliterate the feeding vessel. Because of the occurrence of post-banding deep ulcers and consequent risk of bleed, of the difficulty in band deployment in the acute setting because of limited visibility from the banding hood, and since there are case reports of accidental banding of the major papilla leading to biliary obstruction [87], the use of EVL in ectopic variceal bleed is not indicated.
- *Clipping*: Clipping can be easily applied but has the potential of further increasing bleeding with drawbacks similar to those of banding [88]. The success rate of this technique has not been evaluated in controlled trials and its use is dependent on individual expertise, location of the EcV, and technical feasibility.
- *EUS*: EUS is an important tool for diagnosis, differentiation and guiding the therapy both in the acute setting and on follow-up. It easily localizes and differentiates EcV from other bleeding mucosal lesions [68, 89]. In patients with rectal varices, EUS is more sensitive than routine endoscopy—the EcV are seen as round or ovoid, tortuous, anechoic structures with an increase in the size of submucosal and perirectal vessels without associated wall thickening or without necessarily detecting the presence of perforating veins [90–92]. EUS can guide the injection of sclerosants, glue or thrombin, and help deciding both the amount and the site for injection, or the deployment of coils when adequate visualization is not possible due to active ongoing bleed [93, 94]. EUS is also useful in the follow-up of the varices after endoscopic therapy, as it can detect residual varices, perforating veins, and collaterals; EUS can also guide further session of endoscopic therapy and may decrease the risk of bleeding [8].

- *Step 3—interventional radiology techniques* (*rescue therapies*): TIPS is an attractive option based on the principle of decreasing portal pressure as the underlying cause of bleeding EcV is increased portal pressure [95–98]. In a case series, TIPS led to a decreased need for repeated procedures in patients with EcV, including peristomal varices, with rebleeding rates in this group averaging 23

and 31 % at 1 and 2 years, respectively [98]. In a series of 28 patients by Kochar et al. [99], TIPS achieved 100 % initial hemostasis in all patients with ectopic variceal bleed. The rate of rebleeding was 21 % (5 out of 28). Of these, two were due to shunt dysfunction. TIPS with concomitant variceal embolization is preferred to reduce rebleeding. TIPS use should be considered taking into account the risk of hepatic decompensation and encephalopathy [100] and may not be suitable for EcV caused by focal venous obstruction.

BRTO is another option. In a case series by Watanabe et al. [58] BRTO was shown to be successful in occlusion of the feeding vessels in EcV.

PTO is another rarely performed procedure in which coil embolization of the veins draining into the EcV is performed by transhepatic route. Use of PTO for duodenal varices [101], rectal varices [102], jejunal varices (using transhepatic portovenous angioplasty and stenting) [103], and for the treatment of peristomal varices has been reported.

- *Step 4—surgical interventions*: If endoscopic techniques and interventional radiologic procedures fail to control bleeding or are not feasible, surgery is the next step for management. It is preferred in patients with Child-Pugh A cirrhosis and in patients with an EHPVO.

  The various options include surgical resection or ligation of ectopic bleeding varices [104, 105], splenectomy for EcV secondary to splenic vein thrombosis from chronic pancreatitis [106, 107]. Minor interventions include simple oversewing of duodenal varices through a duodenotomy [108] duodenal dearterialization and stapling, circumferential-stapled anoplasty [109].

  In patients with peristomal varices, local measures such as the initial application of manual pressure and positioning the patient in a recumbent position are usually effective. Ligation or cautery is also effective if bleeding vessels are visible [84]. An attempt for surgical revision or relocation of the stoma is usually ineffective and recurrence of bleeding is common. Portosystemic shunt surgery is highly successful in control of bleeding [110, 111] and has the lowest incidence of rebleeding and need for additional procedures compared with other interventions [112], but at the same time the increased operative risk from the underlying liver disease and a potential for hepatic decompensation are matters of concern.

  In rectal varices, surgical staples have been used successfully [113, 114]. Depending on the cause and degree of liver dysfunction, liver transplantation may be the last resort for correcting the underlying PHT with restoration of normal liver function.

  Rupture of an intraperitoneal varix is a rare entity and a high index of suspicion is required for diagnosing it as described in Fig. 14.1. Surgical exploration attempting to locate and ligate the bleeding varix may represent the only option [115].

  The stepwise approach adopted from Sarin and Kumar et al. is shown in Figs. 14.7a–f and 14.8a–f.

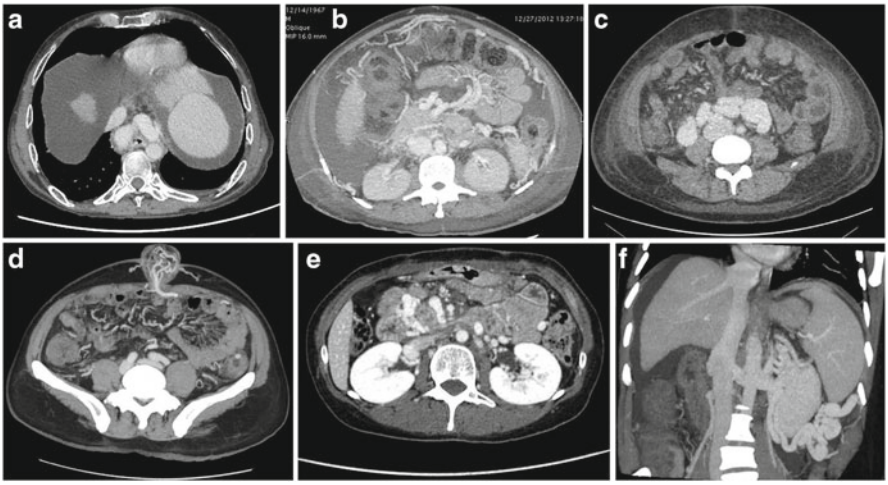

Fig. 14.7 (**a**–**f**) Portosystemic collaterals. (**a**) Paraesophageal. (**b**) Omental. (**c**) Retroperitoneal. (**d**) Umbilical. (**e**) Paraduodenal. (**f**) Lienorenal

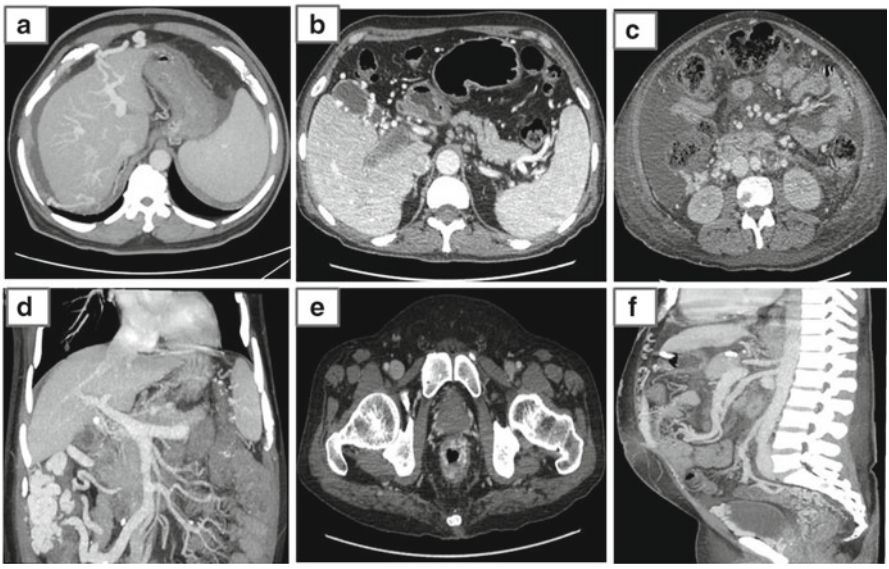

Fig. 14.8 (**a**–**f**) Portosystemic collaterals. (**a**) Intrahepatic collaterals and recanalized paraumbilical vein. (**b**) Pericholecystic. (**c**) Perirenal. (**d**) Pericolonic. (**e**) Perirectal. (**f**) Perivesical and perirectal with patent inferior mesenteric vein

Prophylaxis

The available literature does not suggest either primary or secondary prophylaxis for the ectopic varices.

Conclusions

Bleeding from EcV is rare and often difficult to diagnose, and hence requires a high index of suspicion and is associated with high mortality (i.e., up to 40 %). Management requires multimodal imaging or repeated endoscopies. The management of acute ectopic variceal bleed requires a multidisciplinary approach that includes pharmacological, endoscopic, and angiographic methods with surgery for highly selected cases. To determine the best treatment modalities and their outcomes, large randomized controlled trials are required.

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Chapter 15
Should We Be Concerned About Coagulation in the Treatment of Acute Variceal Hemorrhage?

Armando Tripodi

Introduction

Coagulation factors are synthesized by the liver and most of them are reduced in the event of synthetic impairment subsequent to chronic liver disease (cirrhosis) [1]. Over the years it has been taken for granted that reduced levels of coagulation factors are associated with the occurrence and recurrence of gastrointestinal hemorrhage or hemorrhage during liver biopsy and other invasive procedures. This belief and the practical implications that necessarily follow are difficult to be dismantled, notwithstanding accumulating opposite evidence. This chapter aims at discussing why this belief is not evidence-based.

The Rise and Demise of a Dogma

Cirrhosis is characterized by reduced synthesis of coagulation factors as well as by thrombocytopenia and for these reasons has been considered for long time as the prototype of the acquired coagulopathies. Consequently, the bleeding tendency associated with the disease has been causally related with the abnormality of coagulation tests and the practice of screening patients with traditional hemostasis tests such as the bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT), and platelets count have been implemented. Abnormalities of these tests have been (and are still) considered as indexes to predict bleeding and, as a

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consequence, patients who present with values outside predefined cut-offs are treated with plasma, coagulation factor concentrates, or platelets aimed at correcting the observed abnormalities in the belief that surgery, biopsy, or invasive procedures would be safer. As mentioned, this practice has been largely based on biological plausibility and much less on evidence from clinical trials. One would therefore wonder whether patients with cirrhosis need to receive prophylaxis or rescue therapy with any of these agents. The following sections discuss the pro and contras of infusing coagulation factor concentrates, plasma, or platelets in patients with cirrhosis.

Coagulation Factor Concentrates

Recent controlled randomized clinical trials showed that treatment with recombinant activated factor VII (one of the most potent procoagulant agents) was poorly effective in stopping variceal bleeding in patient with cirrhosis [2, 3], or in decreasing transfusion requirements in patients undergoing surgery [4, 5], in spite of the fact that the treatment was effective in normalizing pre-infusion abnormal PTs [2]. These results appear to indicate that the PT is not representative of the coagulation process operating in vivo. Furthermore, these observations are in line with the new concept that is emerging from the recent literature. In 2005 it has been shown that plasma from patients with compensated cirrhosis, when investigated with laboratory tests reflecting the function of both the pro- and anticoagulant drivers of coagulation, generates normal amounts of thrombin [6], if patients are not severely thrombocytopenic [7] and this occurs notwithstanding the fact that the PT is considerably prolonged. These observations support the conclusion that the conventional coagulation tests (PT and allied tests) are unsuitable to represent the coagulation system as it occurs in vivo in cirrhosis and perhaps in other acquired coagulopathies [8]. These observations can be taken as an explanation for the poor ability of the PT as a predictor of bleeding in patients with cirrhosis that was underscored for many years (reviewed in ref. [9]). Furthermore, these observations explain the poor efficacy of procoagulant agents in controlling bleeding in cirrhosis as shown by the afore-mentioned clinical trials [2–5]. As a matter of fact, if thrombin generation is basically normal, it should not require to be increased by infusion of procoagulant agents. The reasons why thrombin generation is normal and the PT is not a good predictor of bleeding probably rest on the fact that coagulation in cirrhosis is rebalanced owing to the concomitant reduction of pro- and anticoagulant factors [8, 10]. The PT and allied tests, in spite of being considerably prolonged in this condition, do not predict bleeding because they are responsive to the thrombin generated as a function of the reduced procoagulant factors, but much less to the parallel reduction of the anticoagulants [8, 10], especially protein C and antithrombin, which are poorly activated in the absence of thrombomodulin [11] or glycosaminoglycans, respectively. Thrombomodulin and glycosaminoglycans are located on endothelial cells, but not in plasma. Accordingly, it has been shown that thrombin generation in

cirrhosis is considerably reduced when testing is performed in the absence of thrombomodulin, but becomes normal when testing is performed in the presence of thrombomodulin [6, 7].

Fresh Plasma

No data stemming from controlled clinical trials are available to judge the efficacy of infusion of fresh frozen plasma in patients with cirrhosis. Recently, plasma samples from patients with compensated cirrhosis have been added in vitro with appropriate amounts of a pooled normal plasma in order to achieve a proportion patient-to-normal plasma equivalent to the proportion that would have been obtained in the circulation of patients receiving an infusion of 15 mL/kg fresh plasma (i.e., the dose commonly used for patient treatment) [12]. The mixture was freshly tested for PT, APTT, and thrombin generation. The results showed that the PT and APTT, which were abnormally prolonged in the majority of patient plasmas before mixing, were shortened to a considerable extent, but did not normalize completely when mixed with the pooled normal plasma [12]. Conversely, thrombin generation in the presence of thrombomodulin, which was within normal limits in all plasmas prior to mixing, remained substantially unchanged after mixing [12]. These results question the validity of the PT as a test to guide transfusion of fresh plasma in the setting of cirrhosis. Although randomized controlled trials with clinical end points are needed to substantiate this hypothesis, it is unlikely that fresh frozen plasma, given at the dose commonly employed (i.e., 15 mL/kg), can be effective in substantially increasing thrombin generation. However, it cannot be excluded that plasma infusion, by increasing both the pro- and anticoagulants, could be effective in stabilizing the (unstable) balance of coagulation in these frail patients. Nevertheless, according to the afore-mentioned results, this can be reasonably obtained only by infusing such an amount of plasma that would result in fluid overload and exacerbation of portal hypertension.

Platelets

Platelets exert different and composite roles in hemostasis. They adhere to the subendothelial matrix at the site of vessel wall injury by means of the adhesive multimeric protein von Willebrand factor. After adhesion, platelets undergo activation, shape-change, and secretion that eventually lead to aggregation. In a third step, platelets expose on their surface negatively charged phospholipids that, acting as receptors for vitamin K-dependent coagulation factors, speed up thrombin generation and fibrinogen-to-fibrin conversion. Because of the variable thrombocytopenia that is associated with cirrhosis, it is generally thought that these properties of platelets in this setting are hampered, and that therefore platelet counts before invasive

procedures should be restored to prevent bleeding [13]. However, neither the threshold platelet count that would indicate the need for infusion nor the target platelet count to be obtained after infusion is known. To make things worse, reliable hemostatic tests guiding transfusion are not available. However, it was shown that patients with cirrhosis display platelet adhesion in a flowing system (mimicking the conditions that occur in vivo) similar to that of healthy subjects, despite the fact that these patients are thrombocytopenic. The explanation for this apparent paradox rests on the high levels of von Willebrand factor, typically observed in these patients [14]. More recently, it was shown that even thrombin generation in platelet-rich plasma from patients with cirrhosis is normal if platelet count is higher than 60×10^9/L [7]. All in all, the afore-mentioned observations could be taken as indications that patients with cirrhosis do not need to be infused with platelets unless they are severely thrombocytopenic. However, a recent study showed that infusion of one single adult platelet unit was hardly able to increase substantially the platelet count of patients with cirrhosis with pre-infusion values of 50×10^9/L or less [15]. Furthermore, neither thrombin generation in platelet-rich plasma nor thromboelastometry parameters in whole blood were significantly increased after platelet transfusion [15], thus indicating that if a substantial platelet increase is deemed useful, multiple transfusion would be required. As an alternative, sustained platelets increase could be obtained with treatment with such agonists of the thrombopoietin receptors as eltrombopag. However, a recent clinical trial showed that this can be effectively achieved but at the expenses of increasing the risk of thrombosis [16]. Therefore, decision in individual patients should be made by careful consideration of the risk/benefit ratio [17].

Hypercoagulability in Patients with Cirrhosis

As mentioned previously, thrombin generation is down-regulated by thrombomodulin, the main physiological activator of plasma protein C [11]. This is evident by testing plasmas from healthy subjects in which the difference between thrombin activity generated in the absence and the presence of thrombomodulin amounts approximately to 50 % [18]. The corresponding activity observed in plasma from patients with compensated cirrhosis amounts to approximately 30 % [18]. These observations indicate that plasmas from patients with cirrhosis are partially resistant to the anticoagulant action of thrombomodulin. This resistance appears to result from the increased levels of factor VIII (one of the most powerful procoagulant drivers) and the parallel decrease of protein C (one of the most powerful anticoagulant drivers) [19, 20]. This plasma hypercoagulability, if truly representative of what occurs in vivo, could have important practical implications. Patients with compensated cirrhosis would display hyper- rather than hypo-coagulability [19, 20] and this could explain the increased risk of peripheral and splanchnic venous thromboses, previously observed in retrospective studies [21] and then confirmed by population-based, case–control studies [22] showing that patients with liver disease (cirrhotic and non-cirrhotic) have a twofold increased relative risk of venous

thromboembolism compared to the general population. That risk is even higher when the analysis is restricted to patients with idiopathic events [22].

Recently, it has been shown that the degree of procoagulant imbalance associated with compensated cirrhosis can be assessed by paired thrombin generation tests performed in the presence versus the absence of thrombomodulin [19] or Protac [20], the latter being a snake venom extract acting in vitro as an activator of protein C in a manner similar to that of thrombomodulin. The results of these thrombin generation assays can be expressed as the ratio between the thrombin generated in the presence and the absence of thrombomodulin [19] or as the percentage of thrombin inhibition induced by the presence or absence of Protac (i.e., Protac-induced coagulation inhibition, PICI%) [20]. By definition, the higher the ratio or the lower the PICI%, the greater the procoagulant imbalance. Such assays have shown that the procoagulant imbalance increased with the severity of cirrhosis [19, 20], being intermediate in patients of the Child A–B and relatively high in patients of the Child C class.

These observations, which were independently confirmed by other groups [23, 24], suggest that patients with cirrhosis, especially those who are on the waiting list for transplantation, should be considered for primary antithrombotic prophylaxis. Indeed, these patients are at increased risk of portal vein thrombosis [25–27] that, although being not an absolute contraindication for transplantation, may expose them to a poor post-transplant prognosis. A recent study provided evidence that prophylaxis with subcutaneous low molecular weight heparin was effective (and safe) in preventing portal vein thrombosis in cirrhosis [28]. Other drugs that can be used for prophylaxis (and treatment) of portal vein thrombosis are vitamin K antagonists (VKA). However, since the procoagulant imbalance in cirrhosis is most likely due to the increased levels of factor VIII, combined with the reduced levels of protein C [19, 20], it could be speculated that VKA are not the drugs of choice. Protein C is a vitamin K-dependent protein; therefore, VKA might reduce further this naturally occurring anticoagulant, thus increasing the risk of thrombosis especially in the initial phase of the therapy if high doses of VKA are used. Perhaps, the direct thrombin or factor Xa inhibitors (dabigatran, rivaroxaban, or apixaban) [29] owing to their different action might be more effective and safe than VKA in this setting. Furthermore, unlike VKA, these drugs do not require dose-adjustment by laboratory test; hence, they would also help resolving the problem of the international normalized ratio, whose validity in patients with cirrhosis has been questioned [30]. However, clinical trials are needed to evaluate the effectiveness and safety of the direct oral anticoagulants in patients with liver disease.

Conclusions

Coagulation in patients with compensated cirrhosis appears to be rebalanced owing to the parallel reduction of pro- and anticoagulants. Hence, the hemorrhagic tendency occasionally observed especially in patients with end stage disease should be explained by different mechanisms. It should be recognized that, although rebalanced, coagulation is not as stable as in healthy individuals and that small

alterations may tip the balance towards hypo- or hypercoagulability resulting in hemorrhage or thrombosis depending on circumstantial risk factors.

Infusion of recombinant activated factor VII proved to be poorly effective in randomized clinical trials of patients with cirrhosis who were bleeding from esophageal varices or during hepatectomy [2–5] and might also be contraindicated because of the potential thrombogenicity. Although randomized clinical trials of fresh frozen plasma in cirrhosis are not available, the practice of infusing plasma prior to invasive procedures is rather common. It should, however, be considered with caution because of the risk of fluid overload and the possible exacerbation of the hemodynamic alterations subsequent to portal hypertension.

Thrombocytopenia might be another risk factor for bleeding, but platelet counts as low as 60×10^9/L are adequate to ensure normal thrombin generation in vitro [7]. Furthermore, the increased levels of von Willebrand factor, which are a typical feature of patients with cirrhosis, would restore in vitro platelets adhesion and aggregation [14]. Current guidelines suggest that platelets should be the major concern before undertaking liver biopsy and their numbers should be increased if lower than 60×10^9/L [13]. However, these recommendations are based on evidence stemming from in vitro studies and no firm recommendations can be given on the numbers of platelet to be achieved for a safe procedure. A recent trial comparing eltrombopag with platelet transfusion in patients with cirrhosis undergoing elective invasive procedures showed that none of the patients in either group experienced bleeding [16]. Eltrombopag was effective in avoiding platelet transfusion in many patients, but at the expenses of an increased risk of thrombosis [16]. Hence, decision on platelet increase in individual patients should be made by careful consideration of the risk/benefit ratio [17].

In conclusion, the reasons why patients with end stage liver disease occasionally bleed should be searched for by looking more carefully at the underlying conditions superimposing the rebalanced (but unstable) hemostasis of these patients. Portal hypertension, bacterial infections, endothelial dysfunction, and renal failure are the most promising candidate to look at. It is tempting to speculate that efforts devoted at their investigation and treatment should result in a better prevention/control of bleeding than the correction of the hemostatic abnormalities suggested by the conventional laboratory tests.

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Part IV
Prevention of Rebleeding

Chapter 16
Variceal Rebleeding: Drugs, Endoscopy or Both

Flemming Bendtsen, Søren Møller, and Aleksander Krag

Abbreviations

EIS	Endoscopic injection sclerotherapy
EVL	Endoscopic variceal ligation
HVPG	Hepatic venous pressure gradient
ISMN	Isosorbide mononitrate
NSBB	Non-selective β-blocker
PICD	Paracentesis-induced circulatory dysfunction
RCTs	Randomized controlled trials

Introduction

Bleeding from oesophageal varices is a severe complication of portal hypertension [1]. After initial control of acute variceal bleeding, patients still carry a high risk of rebleeding [2]. Without further treatment after the initial control of bleeding up to 60–70 % will experience a rebleeding episode within 1 year [3]. Among those patients that do rebleed, the mortality is 20–35 % [4]. Preventive procedures are,

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therefore, required in patients surviving an episode of acute variceal bleeding. The risk of rebleeding is highest within the first 6 weeks after the initial bleeding episode, and although the 6 weeks mortality has decreased from approximately 40 % four decades ago to 15–20 % in the last decade, mainly because of improvement in mortality day 0–5, the close association between rebleeding and mortality demands on an increasing focus on improvement in prevention of rebleeding [1, 5]. Historically, prevention of variceal rebleeding was first approached by means of porto-caval surgical shunts [6]. These procedures were very effective in the prevention of variceal rebleeding, but as demonstrated in the first randomized controlled trials (RCTs) in the field of hepatology, shunting was associated with unacceptable rates of disabling encephalopathy without significant effect on survival [7].

Endoscopic procedures as prophylaxis against variceal rebleeding were introduced 30–40 years ago. Several controlled trials showed that sclerotherapy was superior to conservative treatment without endoscopic procedures with respect to risk of rebleeding and, when pooled in meta-analysis, also to improve survival [8–10]. During the last 2 decades, endoscopic variceal ligation (EVL) has replaced endoscopic injection sclerotherapy (EIS) as the endoscopic treatment of choice in the management of rebleeding of oesophageal varices [11, 12].

In 1980 Lebrec et al. showed that treatment with the non-selective β-blocker (NSBB) propranolol was able to reduce portal pressure in patients with portal hypertension and oesophageal varices [13]. Several randomized studies showed that propranolol was capable to reduce the risk of variceal rebleeding and pooling of RCTs has confirmed that propranolol also improves the survival rate [14–16]. Later, the addition of isosorbide mononitrate (ISMN) to treatment with propranolol or nadolol alone was shown to be superior to treatment with propranolol alone with respect to lowering effect on portal pressure [17–19]. More recently carvedilol, which acts by combined blockade of both α and β receptors, has been introduced as treatment against variceal rebleeding [16, 20, 21]. The observation of pharmacological therapy to be able to reduce the risk of variceal rebleeding and improve survival has led to numerous trials, where pharmacological treatment, endoscopic treatment or the combination hereof has been conducted in order to improve long-term outcome after variceal bleeding.

The aims of the present chapter are to thoroughly review the available literature with respect to pharmacological treatment, endoscopic treatment and the combination hereof as prophylaxis against variceal rebleeding.

Pharmacological Treatment

Non-selective β-Blockers

Propranolol and nadolol are the most commonly used beta-blockers. These drugs are non-selective β-blockers (NSBBs) that reduce portal pressure through a reduction in portal and collateral blood flow [22, 23]. Animal and human catheterization

studies have shown that treatment with an NSBB was superior to treatment with a cardioselective beta-blocker [24]. The β-1 effect causes a negative inotropic effect with a reduction in cardiac output leading to a decrease in splanchnic inflow and thereby a reduction in the portal venous flow and pressure and collateral flow. The β-2 effect blocks the splanchnic arteriolar vasodilatation, thereby leading to a further decrease in portal pressure, and due to this additional effect NSBBs are more effective than cardioselective β-blockers. Nadolol seems to have the same effects as propranolol on splanchnic haemodynamics [25] and on the risk of rebleeding and reduction of mortality [26]. The effect of propranolol and nadolol on portal pressure is only moderate with a mean reduction on the hepatic venous pressure gradient (HVPG) of approximately 15 %. Observational studies and RCTs have shown that a reduction of HVPG to below 12 mmHg or by ≥20 % from baseline in patients under drug therapy is associated with a marked decrease in risk of rebleeding [27]. If these reductions in portal pressure are achieved patients do not need additional therapy as prophylaxis against variceal bleeding (evidence1a, A). However, only approximately 35–40 % of patients treated with an NSBB will attain a sufficient reduction in portal pressure of 20 % or to a value below 12 mmHg. Furthermore, a recent study indicates that the initial long-term effect on portal pressure is lost in up to 40 % of patients after a period of 2–3 years [28].

Hepatic venous catheterization requires skilled personnel to be performed and is routinely performed only in highly specialized departments, although the procedure does not require expensive equipment and is rather simple to perform in experienced hands. We would advocate for it to be more uniformly introduced in clinical practice in order to indirectly assess portal venous pressure. This procedure clarifies whether a patient responds with a relevant drop in portal pressure on a specific drug therapy and allows to tailor individual evidence-based pharmacological therapy for the patient, who is a candidate for prophylactic therapy against variceal haemorrhage.

Treatment with either propranolol or nadolol as secondary prophylaxis reduces the risk of rebleeding by approximately 40 % (from about 63 to 43 %) and 5 patients need to be treated to prevent one bleeding episode. The 1-year mortality rate is reduced from around 27 to 20 % and approximately 14 patients need to be treated to prevent one death [29, 30]. Apart from reduction in bleeding-related death, the beneficial effect on mortality could also be attributable to a beneficial effect on bacterial translocation and thereby to the reduction of the risk of development of spontaneous bacterial peritonitis [31]. Interestingly, treatment with an NSBB has recently been shown to reduce the intestinal permeability in patients with portal hypertension. Furthermore, this effect seemed to be independent of the effect on portal pressure [32]. This reduction in intestinal permeability together with the well known effect on gastrointestinal transit-time [33] questions whether treatment with beta-blockers should be limited only to patients, who haemodynamically respond to beta-blockers.

The treatment should be initiated as soon as possible after the patient has been stabilized after the bleeding episode (typically within 1 week) [34]. Initial dose of propranolol is 40 mg daily (in 1–2 doses) and should be increased every 3–5 days with 40 mg to the maximal tolerated dose, which should not exceed 320 mg daily.

Systolic blood pressure should be kept above 90 mmHg and heart rate should not drop below 55 beats per minute. The nadolol dose is approximately 50 % lower than propranolol dose.

Special caution should be taken in patients with decompensated cirrhosis. In an observational study of patients with severe ascites of whom many had renal and electrolyte abnormalities, propranolol was associated with an increased mortality [35]. However, more than half of the patients received a dose of 160 mg per day—a very high dose with potential deleterious effects in this patient group, which have almost universal systemic hypotension at baseline. The same authors then performed a crossover study with 10 patients with refractory ascites, which showed that 8 patients on propranolol developed paracentesis-induced circulatory dysfunction (PICD), while only one developed it when propranolol was withdrawn [36]. Also, in this study, 7 patients received a daily dose of 160 mg of propranolol. Whether this high dose might explain the higher mortality rates and risk of PICD needs to be confirmed. However, it can be concluded that dosing in these patients should be done much more cautiously not exceeding 80 mg per day.

Contraindications to treatment with a non-selective β-blocker are obstructive lung disease, severe untreated heart insufficiency and heart conductance abnormalities. Special care should be taken in patients with diabetes mellitus.

In conclusion, treatment with a non-selective β-blocker as prophylaxis against variceal rebleeding should be considered in all patients experiencing their first variceal bleeding episode.

Nitrates

Isosorbide mononitrate (ISMN) acts as a nitric oxide donor within the liver; its vasodilatory action reduces intrahepatic resistance and porto-collateral resistance [17, 37], which in turn lead to improvement in hepatic blood flow and a reduction in portal pressure. The effects of nitrates on HVPG are only modest with a decrease of 10–12 % [38]. Interestingly, the effect seems to be additive to the effect of propranolol on HVPG, and the combination of these two pharmacological principles seems therefore to be attractive as treatment against variceal rebleeding [39]. Although, nitrates do reduce the porto-collateral resistance, this reduction seems not to be followed by an increase in variceal pressure and flow, since treatment with isosorbide mononitrate was accompanied by either no effect or a decrease in azygos blood flow, which reflects the collateral flow and by a decrease in variceal pressure [37].

ISMN in combination with NSBB has been compared with propranolol without showing any additional effect on risk of mortality and rebleeding [40–42]. The combination therapy of a beta-blocker and ISMN has also been compared to endoscopic therapy without showing difference in effect on variceal rebleeding, but surprisingly a lower mortality rate in the pharmacologically treated patients was found [42]. The beneficial effect of the medical therapy on mortality was unrelated to bleeding, and

other causes such as positive effects of a beta-blocker on the risks of infections might explain the finding. Many of the studies lack the power to detect an additional effect and there is a need of large prospective trials comparing treatment with a non-selective β-blocker alone with the combined therapy of a beta-blocker and ISMN.

ISMN should be administered in low doses due to the risks of side effects. The initial dose is recommended to be 20 mg and should be increased in a stepwise manner with 10–20 mg per 3–5 days to a maximum dose of 80 mg daily.

Treatment with ISMN is associated with the risk of development of arterial hypotension. A recent meta-analysis [42], however, did not find an increased incidence of hypotension in patients randomized to ISMN, but an increased number of patients randomized to the combination therapy of ISMN and beta-blockers had adverse effects leading to withdrawal of study medication compared to patients randomized to beta-blockers (96/251 versus 57/251), especially headache being a frequent cause.

In conclusion, treatment with ISMN potentiates the effect of a beta-blocker on HVPG. Whether this effect can be transferred to reduction in risk of rebleeding and death in patients with previous bleeding remains to be demonstrated. Treatment with ISMN or addition of treatment with ISMN to a beta-blocker can be considered in patients with lack of haemodynamic response to beta-blockers.

Carvedilol

Carvedilol is a non-selective β-blocker with the same effects as propranolol, timolol and nadolol. However, unlike the other beta-blockers, carvedilol also has a vasodilatory effect, because of an intrinsic alpha-adrenergic blocking effect with a capacity to enhance the release of the powerful vasodilator nitric oxide [43, 44].

Three studies have evaluated the long-term effect of carvedilol on HVPG compared to propranolol [20, 45, 46] (Table 16.1). Carvedilol was found to be superior to propranolol in two studies with a reduction of HVPG of 19 % compared to a reduction with propranolol of 12–13 %, while the last study, which only had a short follow-up of only 1 week, showed no difference in the effect between carvedilol and propranolol on HVPG. More importantly, a significantly higher number of patients treated with carvedilol achieved a reduction of HVPG either ≥20 % or to a value below 12 mmHg (37 of 63; 59 %) compared to propranolol (18 of 52; 33 %). In earlier studies, special concern has been raised with respect to the development of hypotension during treatment with carvedilol, primarily owing to rather high doses applied in the early studies [47]. In two of the studies that assessed the effects of carvedilol versus propranolol, mean arterial blood pressure dropped, but in no case the treatment had to be stopped due to this effect. These studies also show that no additional effect seems to be achieved by the increase of carvedilol to a dose above 12.5 mg daily.

Table 16.1 Studies evaluating long-term effect of carvedilol compared to propranolol on splanchnic and systemic haemodynamics

	Banares et al. [45]		De et al. [46]		Hobolth et al. [20]	
	Carvedilol	Propranolol	Carvedilol	Propranolol	Carvedilol	Propranolol
Number of patients	24	22	18	18	21	17
Follow-up time (days)	77	77	7	7	90	90
Carvedilol/propranolol dose (mg)	31 ± 4	73 ± 10	12.5	80	14 ± 7	122 ± 64
Baseline HVPG (mmHg)	19.0 ± 1.1	20.3 ± 0.9	19.0 ± 3.8	16.6 ± 4.0	17.6 ± 4.2	18.4 ± 3.6
End of treatment HVPG (mmHg)	15.2 ± 0.8	17.6 ± 0.7	13.6 ± 5.4	13.1 ± 5.3	14.1 ± 4.0	16.1 ± 4.3
Reduction HVPG (%)	*19**	*12**	*28**	*21**	*19**	*13**
Response rate ≥20 % or to <12 mmHg (%)	*54*	*23*	*61*	*65*	*62*	*41*
Baseline HR	79.9 ± 3.7	77.3 ± 2.6	86.9 ± 13.3	92.6 ± 11.9	82.4 ± 15.2	81.2 ± 14.4
End of treatment HR	65.6 ± 2.0	58.2 ± 1.0	73.5 ± 9.3	69.6 ± 8.0	67.4 ± 10.5	62.6 ± 9.2
Reduction HR (%)	*18**	*25**	*15**	*25**	*18**	*23**
Baseline MAP (mmHg)	91.4 ± 2.5	88.6 ± 4.5	97.3 ± 10.3	91.9 ± 16.0	97.1 ± 13.4	97.7 ± 8.2
End of treatment MAP (mmHg)	81.2 ± 2.9	83.8 ± 3.1	82.2 ± 12.6	86.2 ± 13.3	92.1 ± 11.2	89.5 ± 10.8
Reduction MAP (%)	*11**	*5*	*16**	*6**	*5*	*8**

* $p<0.05$

Therefore, it is advised that carvedilol should be started at low doses (6.25 mg/day). If tolerated, the dose is increased stepwise up to a maximum daily dose of 25 mg administered twice daily, with special care to avoid development of hypotension. Titration should be performed slowly, increasing the dose at intervals of 1–2 weeks. The drug should be taken in association with a meal in order to slow the speed of absorption and reduce the likelihood of side effects. The dose should not be increased in patients developing symptoms or in whom systolic blood pressure decreases below 90 mmHg or with a systolic blood pressure <90 mmHg or a heart rate <50 beats per minute. Carvedilol has no effect on renal function assessed as glomerular filtration rate [44], but due to its vasodilatory effects plasma volume increases with the risk of increasing oedema and weight gain and in some patients it is necessary to increase the dose of diuretics [48].

Only one study has compared the effect of carvedilol to other pharmacological therapies against variceal rebleeding. Lo et al. randomized 121 patients to treatment either with low dose carvedilol of 6.25–12.5 mg or with propranolol and ISMN. A rather high and equal number of rebleeding of 61 and 60 % occurred, respectively, and no difference in mortality was observed [21]. The high rebleeding rates are most likely due to the fact that the patients were not treated endoscopically with band ligation, which is contrary to international guidelines. However, only one serious adverse event occurred in the carvedilol group, while 17 occurred in the combination group. Carvedilol, therefore, seems to be an attractive pharmacological approach in the prophylaxis against variceal rebleeding. However, we do not believe that it should be given outside clinical studies due to the limited documentation of efficacy [49].

Endoscopic Treatment

After the development of the flexible endoscope and the availability in almost any clinical setting, endoscopic therapy has become an integral part of the handling of oesophageal varices. Local injection sclerotherapy (EIS), which reduced risk of rebleeding and improved survival, was initially the standard therapy [8, 50, 51]. The procedure involves injection of a sclerosing agent, which is associated with a number of complications including oesophageal strictures and is therefore no longer recommended [52]. Later, EVL was introduced and has now become the treatment of choice [53]. This technique is based on the principles of rubber-band ligation of haemorrhoids. The varices are sucked into the device and the oesophageal mucosa and submucosa containing the varices are ensnared by the rubber band causing local ischaemia, scarring and subsequent obliteration of the varices. Pharmacological treatments aim at reducing the portal pressure and subsequently the pressure and flow in the varices. In contrast endoscopic therapy is a local treatment that aims at eradicating the varices and does not change portal pressure. Thus, varices may recur after endoscopic eradication, and surveillance and therapy continue lifelong [54].

Sclerotherapy

Endoscopic sclerotherapy is performed by injection of a sclerosing agent paravariceally or intravariceally either to cause inflammation and eventually fibrosis and scarring or to induce thrombosis of the varix. One to two millilitres are injected on each side of the varix starting from the gastro-oesophageal junction and continued along each varix with an interval of 2 cm between each injection. The procedure is repeated with 1–2 (3) weeks interval until obliteration of the varices is achieved. Follow-up endoscopy is performed at 3 months interval the first 6 months and then with 6–12 months interval to detect and treat recurrent varices.

Band Ligation

EVL is performed with a standard multiple ligation device, most often with five to six rubber bands, that allows delivery of one rubber band at a time. The endoscope with the device is inserted in the oesophagus and placed close to a varix, suction is applied and the band is released over the entrapped varix. The procedure is repeated every 2–3 weeks until varices are eradicated or the varices are so small that rubber bands can no longer be placed, which usually requires 2–4 sessions to obtain [55]. Repeated endoscopy is performed at 3 months interval the first 6 months, with follow-up at 6–12 months intervals to detect and treat recurrent varices.

Sclerotherapy Versus Band Ligation

A number of trials have compared EIS with EVL. The first meta-analyses published in 1995 by Laine et al. showed that EVL was superior in both efficacy and safety [12]. They included seven randomized trials with 547 patients and proved that EVL reduced rebleeding (odds ratio (OR) 0.52, 95 % confidence interval (CI) (0.37–0.74)), mortality (OR 0.67, CI (0.46–0.98)) and risk of oesophageal strictures (OR 0.10, CI (0.03–0.29)). Four patients would need to be treated with ligation instead of EIS to avoid one rebleeding episode, and ten to prevent one death. Furthermore, the number of endoscopic treatment sessions necessary to obtain variceal obliteration was lower, with 2.2 CI (0.9–3.5) fewer treatment sessions needed with EVL versus sclerotherapy. Therefore, the use of sclerotherapy has since been limited and should be abandoned as a treatment option in secondary prevention of variceal bleeding.

Sclerotherapy Combined with Band Ligation

In seven randomized trials with a total of 445 patients the combination of EIS and EVL versus EVL alone in the prevention of variceal rebleeding has been compared [56]. Only one of the trials reported a difference in efficacy in terms of a reduced risk of

variceal rebleeding but not in mortality. A meta-analysis of all seven trials found no additional effect of combining the treatments in the prevention of rebleeding (OR = 1.12, CI = 0.69–1.81) or on survival (OR = 1.1, CI = 0.70–1.74), but significantly more adverse events (9 % in the EVL group and 21 % in the combined group, $p < 0.001$) [56]. The difference was due to a higher frequency of oesophageal strictures in the combined group. Thus, there is no evidence to support the combination of EIS and EVL.

Non-selective β-Blockers Versus Endoscopic Band Ligation

A meta-analysis including 687 patients from six trials comparing EVL with NSBB plus ISMN for secondary prevention found no difference in either gastrointestinal bleeding (OR 0.86, CI (0.43–1.76)) or variceal rebleeding (30 % versus 24 %) [57]. The rate of gastrointestinal bleeding was 39 % in the EVL group and 43 % in the NSBB plus ISMN group. The risk for all-cause deaths in the EVL group (33 %) was significantly higher than in the medical group (27 %) (OR 1.43, CI (1.00–2.05)); however, the rate of bleeding-related deaths was unaffected (OR 1.15, CI (0.62–2.12)) [57].

It should be emphasized, however, that the trials in general only followed patients for 1–2 years, and potential differences in long-term efficacy and safety cannot be ruled out. However, one study followed patients for 8 years and observed a lower rebleeding rate with EVL (47 % versus 80 %, $p < 0.001$) compared to NSBB, but the mortality was lower among patients treated with NSBB (49 % versus 30 %, $p = 0.01$) [58]. The superiority of NSBB to reduce mortality has been confirmed in meta-analyses [30, 59]. It has been suggested that this effect, which is unrelated to bleeding, is a non-haemodynamic effect that reduces the risk of bacterial translocation from the gut and secondary infections [31].

Combined Endoscopic and Pharmacological Treatment

Endoscopic and pharmacological treatments act by different mechanisms by decreasing the portal pressure and eradicating the varices locally as outlined previously. Thus the treatments have additive effects and combinations have been tested in numerous trials. Furthermore, to support a combined approach it can be argued that NSBB protects against rebleeding before the varices are obliterated by ligation and it delays recurrence of varices.

Non-selective β-Blockers Combined with Sclerotherapy

This combination has been studied intensively and the data pooled in a meta-analysis [60]. In subgroup analyses mainly excluding EVL the combination therapy with EIS and NSBB is more favourable than either treatment alone in the prevention

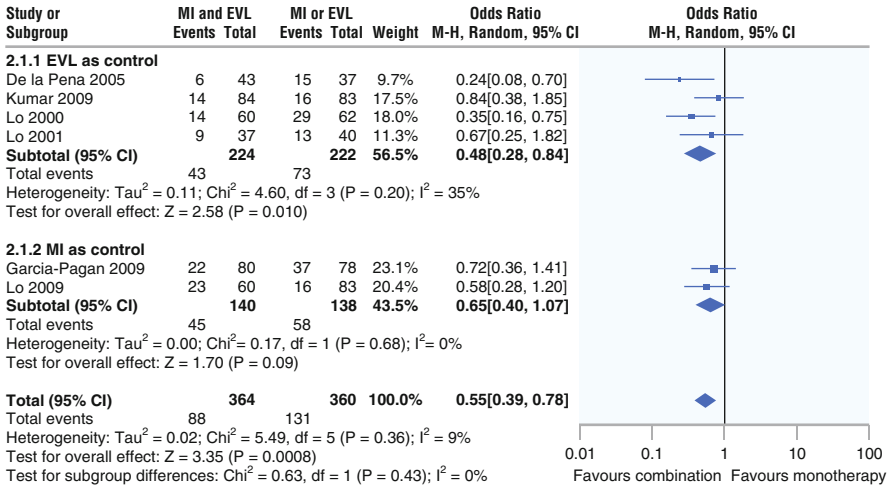

Fig. 16.1 Random effect meta-analysis of overall rebleeding in randomized trials on combination therapy [medical interventions (MI) and banding ligation (EVL)] versus monotherapy (MI or EVL) on secondary prevention in oesophageal varices. (Used with permission from Thiele M, Krag A, Rohde U, Gluud LL. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. Aliment Pharmacol Ther. 2012;35(10):1155–65)

of rebleeding (OR 0.71, CI (0.52–0.96)) but without effect on mortality (OR 0.78, CI (0.0.58–1.07)). However, in this meta-analysis only one full paper and three abstracts on EVL were included. Thus, 19 out of 23 studies included relate to EIS, which as outlined previously should not be used on this indication anymore. Therefore the relevance and validity of this meta-analysis in the era of EVL are limited.

Non-selective β-Blockers Combined with Band Ligation

The majority of current guidelines recommend the combination of NSBB and EVL in the prevention of rebleeding. Nine RCTs have been performed, six with EVL as control treatment and three with pharmacological treatments with NSBB plus isosorbide mononitrate as control treatment. A recent meta-analysis including all trials showed that the combination therapy reduced the risk of upper gastrointestinal rebleeding (OR 0.55, CI (0.39–0.78)) compared to either therapy alone (Fig. 16.1) [59]. The corresponding number needed to treat with combined therapy to prevent one case of rebleeding was eight (95 % CI 5–25). No effect on overall mortality was identified (OR 0.86, CI (0.58–1.27)). Combination therapy reduced bleeding-related mortality (OR 0.52, CI (0.27–0.99); number needed to treat 33 patients) and the risk of oesophageal variceal rebleeding (Fig. 16.2). In subgroup analysis, combination therapy reduced rebleeding compared with EVL (OR 0.48, CI (0.28–0.84)), but not when compared with medical therapy (OR 0.65, CI (0.40–1.07)) (Fig. 16.1). Only two studies provided data for the medical therapy subgroup analysis, however.

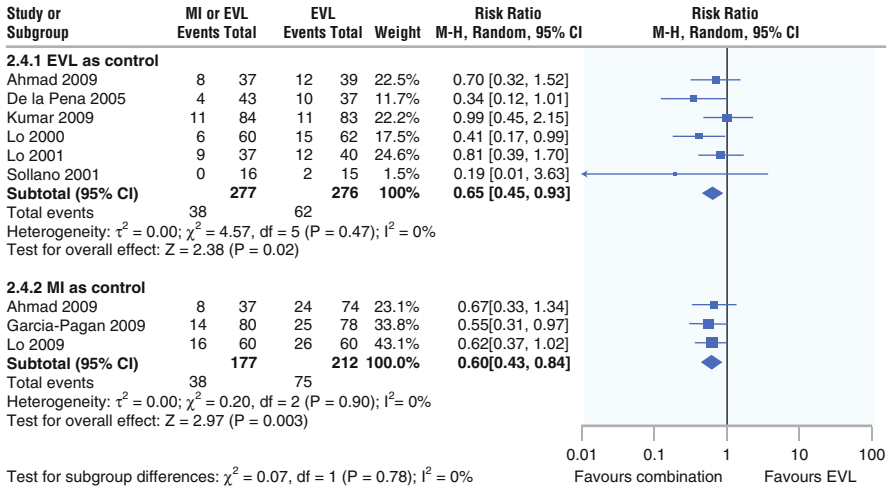

Fig. 16.2 Random effect meta-analysis of oesophageal variceal rebleeding in randomized trials on combination therapy [medical interventions (MI) and banding ligation (EVL)] versus monotherapy (MI or EVL) on secondary prevention in oesophageal varices. (Used with permission from Thiele M, Krag A, Rohde U, Gluud LL. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. Aliment Pharmacol Ther 2012;35(10):1155–65)

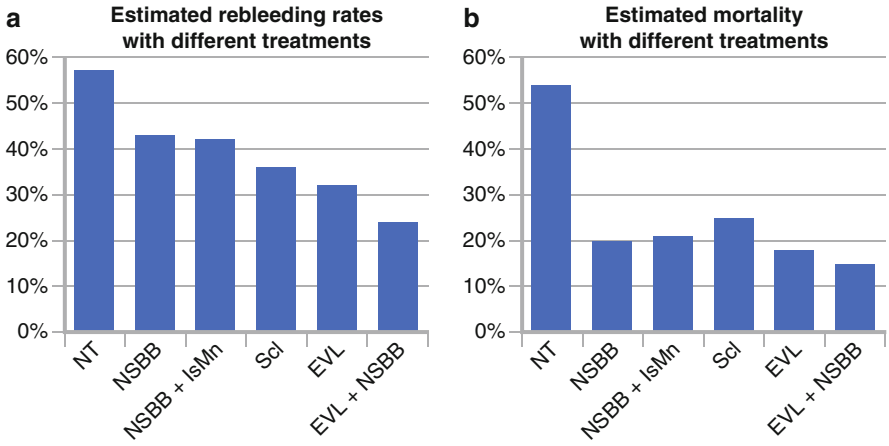

Fig. 16.3 (**a**, **b**) Estimated rebleeding and mortality rates with different treatments used in the prevention of rebleeding from oesophageal varices. Data are obtained from various meta-analyses. *NT* no treatment, *NSBB* non-selective β-blocker, *IsMn* isosorbide mononitrate, *EVL* endoscopic variceal ligation, *Scl* sclerotherapy, *MI* medical interventions

When considering only the risk of variceal rebleeding, this was reduced in both subgroups with EVL or medical therapy as control (Fig. 16.3a, b).

Six trials reported adverse events. The combination therapy and monotherapy did not differ regarding the total number of adverse events (OR 1.69, CI (0.95–2.99)) or

Table 16.2 Meta-analytical data on efficacy and safety of interventions for secondary prophylaxis of variceal bleeding

Study	Intervention	Number of trials	Number of patients	Rebleeding	Mortality	Safety
Bernard et al. [29]	NSBB versus NT	12	769	OR 0.36, CI (0.24–0.53)	OR 0.60, CI (0.42–0.87)	OR 3.69, CI (1.81–7.54)
Laine et al. [12]	EVL versus Scl	7	547	OR 0.52, CI (0.37–0.74)	OR 0.67, CI (0.46–0.98)	OR 0.10, CI (0.03–0.29)
Singh et al. [56]	EVL versus combined EVL and Scl	7	445	OR 1.12, CI (0.69–1.81)	OR 1.1, CI (0.70–1.74)	OR 0.37, CI (0.21–0.62)
Gonzalez et al. [60]	Combined Scl and NSBB versus monotherapy	14	900	OR 0.71, CI (0.52–0.96)	OR 0.78, CI (0.0.58–1.07)	–
Li et al. [57]	EVL versus NSBB	6	687	OR 0.86, CI (0.43–1.76)	OR 1.43, CI (1.00–2.05)	OR, 0.92, CI (0.66–1.28)
Gluud et al. [42]	Combined IsMn and NSBB versus NSBB	5	459	OR 1.04, CI (0.66–1.65)	OR 0.82, CI (0.60–1.11)	OR 1.60, CI (0.78–3.25)
Thiele et al. [59]	Combined EVL and MI versus monotherapy	9	442	OR 0.55, CI (0.39–0.78)	OR 0.86, CI (0.58–1.27)	OR 1.69, CI (0.95–2.99)

Odds ratio (OR) and 95 % confidence interval. Data are obtained from various meta-analyses

NT no treatment, *NSBB* non-selective β-blocker, *IsMn* isosorbide mononitrate, *EVL* endoscopic variceal ligation, *Scl* sclerotherapy, *MI* medical interventions

serious adverse events (OR 2.07, CI (0.92–4.68)). However, there was a clear evidence of inter-trial heterogeneity and meta-analyses using a fixed effect model found more adverse events (OR 1.72, CI (1.23–2.40)) and serious adverse events (OR 2.17, CI (1.17–4.03)) in the combination group. The most common serious adverse events related to banding ligation were bleeding from post-banding ulcers (13 cases). One case of oesophageal stricture necessitating dilation was registered. The most common causes for withdrawal of NSBB were bradycardia, hypotension, dizziness, asthenia, lethargy or fatigue.

Endoscopic and Pharmacological Recommendations for Prophylaxis of Variceal Rebleeding

NSBBs reduce mortality and rebleeding (Evidence 1a, A) and form the mainstay of treatment in the prevention of variceal rebleeding. NSBBs likely have an effect beyond their haemodynamic action that reduces mortality. The lowest rebleeding rate is seen in combined therapy with NSBB and EVL (Evidence 1a, A) (Table 16.2). If tolerated this should be the standard treatment of choice. However, combined therapy does not reduce mortality and increases risk of adverse events including post-banding ulcers. In case of adverse events or intolerance either NSBB or EVL can be used alone. Current evidence does not support an additional effect of adding ISMN, which also increases the risk of adverse events and withdrawals due to adverse events. Carvedilol is a promising treatment, but there are insufficient data to recommend it as treatment against variceal rebleeding.

Rebleeding and bleeding-related deaths are still significant despite the described advances in therapy and warrant further development of treatment modalities.

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Chapter 17
Role of TIPS and Surgery in Prevention of Rebleeding

Christophe Bureau and Jean-Pierre Vinel

Introduction

Although the management of variceal bleeding has been much improved over the last 20 years [1], approximately 17 % of the patients will rebleed within 6 weeks, and 70 % within 2 years [2]. It is therefore mandatory to prevent rebleeding. Using the so-called first-line treatments, namely noncardio-selective beta-blockers and/or endoscopic band ligation, up to 50 % of the patients will still experience rebleeding [3, 4] and will require other therapies.

Porto-caval shunting has consistently been found to be the most effective treatment to prevent variceal bleeding. Shunting has over other treatments the advantage of normalizing portal pressure, which relieves and/or prevents not only rebleeding but also the other complications of portal hypertension. Surgical shunting has been virtually abandoned because of the development of interventional radiology techniques, mainly trans-jugular intrahepatic porto-systemic shunt (TIPS).

Surgery

Surgeons have proven very inventive in designing surgical techniques to relieve portal hypertension or obliterate esophagogastric varices. This suggests that there is no universally good technique which could be recommended for most of the patients. But on the other hand, it allows surgeons to address almost all situations that can be encountered as a cause of variceal bleeding.

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Surgical techniques can be classified into three main categories: shunting techniques (either total or selective), selective variceal decompression, and devascularization procedures.

Techniques

Shunting Procedures

Total Shunting

This can be obtained by end-to-side or side-to-side porto-caval shunts, mesocaval shunts, and proximal splenorenal shunts. Clinical results are grossly similar, with a rebleeding rate below 10 % [5–8]. Rebleeding, in most of the cases, is due to shunt obstruction which ranges from 2 % using side-to-side porto-caval shunts to 18 % in proximal splenorenal shunts [9].

Operative mortality ranged from 1 to 20 % according to the severity of liver failure, after careful selection and preparation of the patients. The main drawback of total shunting procedures was hepatic encephalopathy (HE), mainly chronic, disabling encephalopathy which, in controlled studies, was more frequent in shunted patients than in non-shunted ones [5–8].

Partial Shunting Procedures

This can be obtained using small caliber porto-caval H-graft shunts, as proposed by Sarfeh et al. [10] aiming to maintain a hepatopetal portal flow to preserve liver function and lower the incidence of HE [11]. However, the risk of shunt obstruction is increased in parallel [10]. It may be observed that this technique is a surgical mean to perform what is done by a TIPS through a simple venous puncture.

Selective Variceal Decompression

These procedures were designed with the same purposes: to maintain portal flow towards the liver to preserve liver functions and decrease the risk of HE. The most commonly used approach is the distal splenorenal shunt. However, this procedure, technically more difficult than other shunting operations, failed to prove superior to other techniques, probably because, owing to the persistence of portal hypertension, new collaterals slowly develop.

Another procedure was described by Inokuchi et al. [12, 13]. It drains electively esophageal varices by anastomosing the left gastric vein into the inferior vena cava. However, the procedure is a difficult one and cannot always be performed because of the small diameter of the left gastric vein.

Table 17.1 Controlled trials comparing distal splenorenal shunt (DSRS) and porto-caval shunts (PCS)

	Patients number		Rebleeding rate (%)		Survival (%)		Encephalopathy (%)	
First author (ref)	DSRS	PCS	DSRS	PCS	DSRS	PCS	DSRS	PCS
Rikkers [19]	26	29	4	8	58	62	12	52*
Reichle [20]	14	13	NA	NA	100	78	5	4
Fischer [21]	19	23	11	4	79	100	16	17
Langer [22]	40	38	13	10	51	56	23	40
Millikan [23]	26	29	31	45	31	28	27	75*
Harley [24]	27	27	27	4	43	31	39	32
Grace [25]	38	43	18	12	46	68	39	46

PCS Porta-caval shunt, *DSRS* Distal splenorenal shunt, *NA* not available
*Significant difference

Devascularization Techniques

They aim at reducing blood flow within the varices. Many techniques have been imagined: ligature of the esophagus on a button [14, 15], transection of the esophagus [16] or of the stomach [17], or more sophisticated devascularization procedures such as Sugiura's technique which associates splenectomy, extensive esophagogastric devascularization, and esophageal transection through left thoracotomy and laparotomy [18]. Most of these techniques were designed to stop active variceal bleeding and were not assessed using controlled studies, which precludes any definitive conclusion on their potential advantages over other treatments. However, they should be considered for the treatment of refractory bleeding from extensive portal vein thrombosis which makes derivation procedures impossible to perform.

Results of Surgical Techniques in Preventing Variceal Rebleeding

As a whole, when comparing surgical techniques to one another [19–25], results were grossly similar (Table 17.1), though there was a slight trend towards a lower incidence of HE and better survival in patients treated by selective shunts [4].

Studies comparing surgery to endoscopic sclerotherapy [26–32] (Table 17.2) have been pooled in meta-analyses which showed that shunting was more effective than alternative treatments in preventing rebleeding, though survival was not improved and the incidence of HE was increased [4, 33].

TIPS

The percutaneous trans-jugular route to the liver was first described by W.N. Hanafee and M. Weiner to perform hepatic venography, cholangiography, and liver biopsy. In 1969, in swine, Rösch et al. [34] performed the first intrahepatic

Table 17.2 Controlled trials comparing surgery and endoscopic sclerotherapy (ES)

	Patients number		Rebleeding rate (%)		Survival (%)		Encephalopathy (%)	
First author (ref)	Surgery	ES	Surgery	ES	Surgery	ES	Surgery	ES
Rikkers [26]	27	30	19	57*	39	35	15	20
Teres [27]	57	55	14	38*	71	68	24	8*
Henderson [28]	35	37	3	59*	43	68*	16	12
Planas [29]	34	35	3	40*	83	79	40	12*
Orozco [30][a]	33	46	9	63	NA	NA	NA	NA
Isaksson [31]	24	21	17	57	100	76	18	6
Santambrogio [32]	40	40	15	53	73	56	55	18

*Significant difference

[a]A third group was treated using beta-blockers ($n=40$) in which rebleeding rate was 73 %

porto-systemic shunt. Thirteen years later, Colapinto et al. reported their preliminary experience in patients with the formation of intrahepatic shunts simply dilating the intra-parenchymal tract between the two venous systems with a balloon catheter [35]. However, several cases of fatal intraperitoneal hemorrhages from the rupture of the liver capsule were reported and, given the elasticity of the liver tissue, these shunts occluded within a few days. In order to maintain shunt patency, JC Palmaz used balloon expandable stents [36]. The first TIPS in a human patient was performed by Richter et al. with a Palmaz stent [37]. Thereafter, self-expandable stents, then in 2002 polytetrafluoroethylene (PTFE)-covered stents were made available. The use of the latter device markedly decreased the rate of shunt dysfunction and improved clinical outcome of the patients [38–40]. These technical advances must be kept in mind when evaluating the results of older clinical trials.

Technique

Effective protection against the complications of portal hypertension is obtained whenever hepatic venous pressure gradient is decreased to 50 % of its initial value or below the threshold of 10 mmHg. This should be achieved with the smallest possible stent diameter, hoping to maintain a hepatopetal portal blood flow to reduce the risk of post-TIPS hepatic encephalopathy. Whenever HVPG remains higher than expected a second parallel shunt may be performed. At the end of the procedure, control angiography is carried out. Some authors advocate embolization of collaterals which are still visible after TIPS. However, the effectiveness of such a procedure has not been demonstrated. Furthermore, embolization might lead to portal vein obstruction and/or remote complications such as lung or brain abscesses.

Two specific conditions deserve specific comments:

- In Budd-Chiari syndrome, the TIPS technique is basically the same as long as a hepatic vein stump remains patent and can be catheterized, using US guidance if necessary. In a few patients, hepatic veins are completely obstructed.

Table 17.3 Main contraindications for TIPS

– Age >75
– Child-Pugh score >12 or MELD score >18
– Overt hepatic encephalopathy or history of severe and/or recurrent encephalopathy
– Cardiac failure
– Respiratory failure
– Organic renal failure
– Pulmonary arterial hypertension
– Hydatid cyst
– Polycystic liver
– Dilatation of intrahepatic bile ducts
– Hepatocellular carcinoma
– Complete portal vein thrombosis

In those conditions, the puncture has to be made directly through the anterior wall of the inferior vena cava aiming to enter the left branch of the portal vein through the hypertrophic caudate liver lobe [41]. The puncture route should be embolized after the procedure.

- Portal vein thrombosis was initially considered a contraindication for TIPS. Nowadays, on the contrary, partial thrombosis should be considered an indication since the reversal of blood flow from hepatofugal to hepatopetal may help dissolving the thrombus [42]. Before the procedure, it is mandatory to make sure the thrombosis is due to a clot and not to tumoral invasion. Even if the portal vein is completely obstructed, TIPS can be successfully performed after the clot has been destroyed (by aspiration, fragmentation, or mechanical thrombectomy) or crushed against the vein wall by the expanded stent. The most difficult condition is portal vein cavernoma, in which it may be extremely difficult, or even impossible, to identify a route large enough to release the prosthesis.

Complications and Contraindications (Table 17.3)

In a retrospective series of 1,750 patients, the rate of lethal complications was 1.7 %, ranging from 3 % in centers where less than 150 procedures had been performed, to 1.4 % in more experienced hands [43]. Seven types of complications can be secondary to the shunting itself.

Shunt Dysfunction

This may have two different origins: thrombosis or pseudo-intima over-proliferation. Thrombosis usually occurs within the first 3 weeks. Its incidence ranges from 10 to 15 % [44]. It may be due to a technical problem such as insufficient covering of the intra-parenchymal tract or kinking of the prosthesis. Diagnosis is easy by

Doppler-US. The shunt can be recanalized. Prophylactic anticoagulation has been proposed, but the efficacy of this treatment has not been proven and it may be harmful in patients with deteriorated liver functions and portal hypertension.

Within 3–4 weeks after insertion in the liver, the prosthesis is progressively covered by a smooth layer of fibrous tissue topped by a single layer of endothelial cells. This pseudo-intima prevents thrombosis, but the process can be exaggerated and lead to a narrowing or even total obstruction of the shunt [45]. Such a pseudo-intima overgrowth is the most common cause of shunt dysfunction the incidence of which has been reported to range from 20 to 80 % within 1 year. Over-proliferation may also involve the hepatic vein. In order to detect dysfunction, Doppler-US follow-up was mandatory. Pseudo-intima proliferation is very effectively prevented using PTFE-covered stents since the covering inhibits its development so that the rate of TIPS dysfunction drops below 10 % [38–40].

Liver Infarction

This is a rare complication which can be caused by a lesion or acute thrombosis of the hepatic artery when the portal vein is punctured. Partial Budd-Chiari syndromes were also reported after a hepatic vein had been obliterated by the stent. The risk might be increased with covered prostheses [46].

Cardiac Failure

The sudden increase in cardiac preload by the shunting may decompensate cardiac function. Accordingly TIPS should be contraindicated in patients with an ejection fraction below 50 %.

TIPS Infection

The incidence of the so-called endotipsitis has been reported to be 1.2 % in a series of 165 patients [47]. Long-term antibiotic therapy is not always effective and liver transplantation can be indicated.

Hepatic Encephalopathy

Clinical studies consistently reported an increased incidence of encephalopathy following TIPS. This complication was ascribed to the shunting itself, so that a history of severe or recurrent HE is considered a contraindication for TIPS. Using bare stents, HE usually improves along with the narrowing of the shunt by pseudo-intima proliferation. The incidence and/or severity of this complication was expected to be increased by using covered prostheses with more effective shunting. However, this

was not confirmed by clinical studies. On the contrary, the only published randomized trial reported a lower incidence of HE in patients treated with covered stents [39, 40]. This was ascribed to a significantly less frequent need for hospitalizations, control angiographies, and shunt revisions, and fewer relapses of portal hypertension-related complications. Should incapacitating HE be observed after TIPS, the shunt could be reduced or even totally obstructed using specifically designed devices or a second coaxial stent [48].

Liver Failure

This may be precipitated by the shunting of portal blood flow. The risk is increased in patients with hepatopetal blood flow and those with low arterial flow. Accordingly, TIPS should be contraindicated in patients with severe liver failure as assessed by a Child-Pugh score over 12 or a MELD score over 18.

Hemolysis

This has been reported in up to 30 % of the patients. It is most of the time asymptomatic, except for an increase in unconjugated bilirubin in serum. Hemolysis was ascribed to lesions of erythrocytes on the metallic mesh of the prosthesis and accordingly disappears along with the covering of the stent by a pseudo-intima [49].

Results in the Prevention of Variceal Rebleeding

TIPS was compared to other treatments in 14 studies: sclerotherapy [50–55], band ligation [56–59], endoscopic treatment associated with beta-blockers [60–62], and beta-blockers plus nitrates [63] (Table 17.4). As a whole, meta-analyses [64–66] showed TIPS to be more effective in preventing rebleeding, reducing the risk by approximately 50 % (Table 17.4). However, the incidence of encephalopathy was significantly greater in patients treated by TIPS and survival was not improved.

TIPS was also compared to shunt surgery, 8 mm H-graft porto-caval shunts [67–70] and distal splenorenal shunt [71]. TIPS and surgery were found to be of similar efficacy in preventing rebleeding. However, shunt failures and need for reinterventions were more frequent with TIPS, because of the high obstruction rate of the bare prostheses which were used. Those comparisons should be reassessed using PTFE-covered stents.

The cost-effectiveness of TIPS was another concern [72]. A modeling approach found TIPS to be both more effective and more cost-effective than banding ligation [73]. These results were confirmed by a multicenter study performed in the USA [74], showing that TIPS was actually as effective as distal splenorenal shunt in preventing rebleeding while the use of covered stents proved more cost-effective.

Table 17.4 TIPS vs. endoscopic and/or drug therapy

	Patients number			Rebleeding rate (%)		Mortality rate (%)		Encephalopathy (%)	
First author (ref)	TIPS	Control group	Treatment in control group	TIPS	Control group	TIPS	Control group	TIPS	Control group
Cabrera [50]	31	32	EST	23*	52	7	18	33*	13
Sanyal [51]	41	39	EST	22	21	29*	18	29	13
Cello [52]	24	25	EST	13*	48	33	32	50	44
Merli [53]	38	43	EST	24*	51	24	19	55*	26
Garcia-Villareal [54]	22	24	EST	9*	50	15*	33	23	25
Narahara [55]	38	40	EST	18*	33	29	18	34	15
Jalan [56]	31	27	EBL	10*	52	42	37	36	26
Pomier-Layrargues [57]	41	39	EBL	18*	66	43	44	47	44
Sauer [58]	43	42	EBL	16*	43	26	29	37	21
Gülberg [59]	28	26	EBL	25	27	14	15	7	19
GEAIH [60]	32	33	EST + P	38*	68	50	42	NA	NA
Sauer [61]	42	41	EST + P	23*	57	31	33	29*	13
Rössle [62]	61	65	EST/EVL + P	15*	41	13	12	36*	18
Escorsell [63]	47	44	P + IMN	13*	39	28	28	38*	14

EST endoscopic sclerotherapy, *EBL* endoscopic band ligation, *P* propranolol, *IMN* isosorbide-5-mononitrate
*Significant difference as compared to control group

Indications

Whenever possible, liver transplantation should be considered in these patients whose liver function is usually poor. When it is contraindicated as well as in patients on the waiting list, or the few whose liver function is fairly preserved, a shunting procedure should be considered.

TIPS as well as surgery of portal hypertension are considered second-line treatments for the prevention of recurrent bleeding because they are both more effective in preventing rebleeding but more invasive than drug and/or endoscopic therapies, with a higher risk of complications or side effects, and no clear advantage on survival. However, their efficacy after the failure of other therapies has never been specifically assessed by randomized controlled studies. The difference between "first-line" and "second-line" treatments lies on studies including mostly "first-line" patients.

A French survey [75] showed that 24 % of the patients admitted with recurrent bleeding had not been given any prophylaxis, 4 % had been treated by sclerotherapy, 9 % by band ligation, 28 % by beta-blockers, and 35 % by endoscopic therapy plus beta-blockers. A rebleeding episode may therefore be an opportunity to give the patient a preventive treatment or to change his previous treatment for the optimal recommended one [76].

Nowadays, whenever a shunting procedure is considered needed, TIPS with PTFE-covered stents should be preferred to surgery because it avoids the complications of laparotomy, it does not hamper the chance for transplantation, and it can be reduced in diameter or occluded if needed due to the occurrence of refractory hepatic encephalopathy. Only in the few situations where TIPS cannot be performed, e.g., complete portal vein obstruction or cavernoma, devascularization techniques can be attempted.

Conclusion

Variceal rebleeding does not systematically need switching to shunting therapy. The need for an alternative treatment should be decided according to the severity of the hemorrhage, and of the underlying liver disease, the general status of the patient and comorbidities. If optimal first-line treatment has failed, most of the patients should be treated by TIPS using PTFE-covered stents and considered for liver transplantation whenever possible.

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Part V
Special Situations

Chapter 18
Variceal Bleeding in Patients with Vascular Liver Disease

Dominique-Charles Valla

Introduction

Vascular diseases of the liver include different clinical–pathological entities, several of which share portal hypertension as a main feature [1]. Such vascular liver diseases include Budd-Chiari syndrome, an obstruction of the hepatic venous outflow tract; portal cavernoma, a long-standing obstruction of the portal vein which is replaced by a network of hepatopetal collaterals; and non-cirrhotic idiopathic portal hypertension, a spectrum of various pathological changes causing a blockade of the intrahepatic microcirculation in the absence of cirrhosis. Portal vein thrombosis complicating cirrhosis can be added to this list [1]. An additional, important, and singular feature of these diseases is to be usually caused by thrombosis, which explains a strong association with underlying prothrombotic conditions. These underlying conditions may make anticoagulation therapy necessary for the prevention of recurrent or extensive thrombosis. However, managing the prevention of bleeding due to portal hypertension together with the prevention of thrombotic complications of underlying disease with anticoagulation requires a clear evaluation of the risks and benefits of each therapeutic intervention, and a fine tuning of their balance.

Because the data presently available on the management of variceal bleeding in this context are limited, recommendations for clinical practice cannot be based on solid evidence. The purpose of this chapter based on an overview of data reported since 1990 is to draw some conclusions regarding the management of variceal bleeding in patients with primary Budd-Chiari syndrome, portal cavernoma, idiopathic non-cirrhotic portal hypertension, and portal vein thrombosis of cirrhosis.

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Budd-Chiari Syndrome

Budd-Chiari syndrome is characterized by an obstructed hepatic venous outflow tract. Rarely, obstruction can be secondary to an invasion of the venous lumen by a malignant tumor, mostly hepatocellular carcinoma, but also leiomyosarcoma, or epithelioid hemangioendoblastoma. Control of the neoplastic process is then the major goal for management. Compression secondary to benign lesions, generally simple cysts and focal nodular hyperplasia, is relatively common when these lesions reach a large size and are located high in the liver, near the opening of the major veins in inferior vena cava. Compression secondary to benign lesions is almost never symptomatic, probably because venous collaterals efficiently decompress the liver. Only when compression is associated with hepatic vein thrombosis will there be clinical manifestations and laboratory anomalies.

Thrombosis, Prothrombotic Disorders, and Prophylaxis of Thrombotic Events

In patients with primary Budd-Chiari syndrome, the obstruction of the hepatic venous outflow tract is related to thrombosis of the hepatic veins, suprahepatic inferior vena cava, or both [2]. With time, the thrombosed portion of the veins can transform into a short length stenosis or a fibrous cord. Complications include portal hypertension, ascites, and liver dysfunction. From patient to patient, these features combine variously, and develop over a variable period of time, depending probably on the speed and the extent of the venous obstructive process [2]. Patients without clinical manifestations are characterized by the development of an extensive network of hepatic venous or portosystemic collaterals [3].

In over 80 % of patients with a primary Budd-Chiari syndrome, an underlying risk factor for venous thrombosis is present [2]. The main factors include myeloproliferative neoplasms (accounting for about 50 % of cases), antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and Behcet's disease. All these diseases are regarded as high risk factors for thrombosis, meaning that they should consider permanent anticoagulation therapy. Actually, the risk of extension, recurrence, or involvement of extrasplanchnic veins in untreated patients with such underlying disorders has not been well evaluated because most patients have been placed on long-term anticoagulation therapy. Many other risk factors for venous thrombosis can be documented in patients with primary Budd-Chiari syndrome: exposure to oral contraceptives, factor V Leiden mutation, prothrombin gene mutation, hyperhomocysteinemia, etc. [2]. The latter factors, however, are considered less potent than the former in causing venous thrombosis, and are generally combined with more potent risk factors in affected patients [2].

Portal vein thrombosis is a dreaded complication of primary Budd-Chiari syndrome because it is associated with a worse prognosis and because it compromises key

treatment options such as TIPS insertion and liver transplantation [4, 5]. It is unclear, however, if superimposed portal vein thrombosis makes Budd-Chiari syndrome more severe [6]. Rather, portal vein thrombosis appears to be a marker of a more severe block on the portohepatic venous circulation. Still, the main risk factor for portal vein thrombosis in patients with cirrhosis is the number of underlying prothrombotic conditions combined in the same patient [4].

Anticoagulation has been recommended in all patients with primary Budd-Chiari syndrome in order to prevent recurrence and extension in the hepatic venous outflow tract, portal vein, and extrasplanchnic areas [7–9]. This recommendation is logical in patients with underlying conditions associated with a high prothrombotic potential when this condition cannot be completely and permanently controlled by a specific treatment. However, the impact of this therapy on the risk of thrombosis has not been precisely assessed. This recommendation is mainly grounded on the marked improvement in outcome (5-year survival increasing from 50 ± 8 to 75 ± 6 %) that corresponded to the implementation of routine anticoagulation therapy at one specialized unit [10]. It was also shown in a multicenter retrospective study that anticoagulation therapy was independently associated with improved survival among patients with the best baseline prognosis indices [11]. Furthermore, recurrent thrombosis appears to be rare in treated patients [12]. Actually, 40–60 % of patients have a fully controlled disease with anticoagulation as the only therapy, without a need for invasive procedures to decompress the liver [12, 13].

Bleeding Related to Portal Hypertension and Its Prophylaxis

Gastrointestinal bleeding is one of the possible presentations of the disease. A history of gastrointestinal bleeding was recorded in 5–14 % of patients in recent surveys [3, 6, 10–12, 14–17]. Thus, gastrointestinal bleeding is less common as a presenting feature than abdominal distention corresponding almost always to ascites (about 90 % of patients), and abdominal pain (about 85 % of patients) [3, 6, 10–12, 14–17]. Gastrointestinal bleeding is usually accompanied or rapidly followed by ascites in patients with Budd-Chiari syndrome. Information on the prevalence of esophageal varices is scarce. In the survey by Rajani et al., 9 of 33 patients (27 %) had a history of gastrointestinal bleeding, 4 of 43 (9 %) had bled from varices, and varices had been present in 18 of 27 (67 %) [14]. Esophageal varices had been found in 14 of 31 patients (45 %) by Tan et al. which did not report past gastrointestinal bleeding [15]. Esophageal varices had been found in 45 of 73 patients (71 %) in the study by Seijo et al. which reported gastrointestinal bleeding in 8 of 157 patients (5 %) [12].

The spontaneous risk of recurrent bleeding, and the prognostic factors for it, could not be evaluated as most patients have received some form of treatment to prevent the rupture of varices [6, 12]. For the last 10–20 years, lessons drawn from clinical trials in patients with cirrhosis have been extrapolated to patients with Budd-Chiari syndrome [7–9]. As a result, prophylaxis has usually been applied based on the size of esophageal varices and the presence of red signs, and consisted

of nonselective beta-adrenergic blockade or endoscopic band ligation or both. To the best of author's knowledge, there has been no evaluation of these methods in patients with Budd-Chiari syndrome. Another source of confusion in evaluating the bleeding risk in patients with Budd-Chiari syndrome is that treatment of the disease itself results in a significant hepatic decompression, which is directly translated into a decreased portal pressure gradient [2]. There is some evidence that this can be achieved (1) indirectly through the development of hepatic or portosystemic collaterals, spontaneously [3] or with anticoagulation therapy; or (2) directly by relieving the outflow block through angioplasty of the obstructed hepatic veins or inferior vena cava, or by insertion of a TIPS, or construction of a surgical portosystemic shunt, or by liver transplantation [1, 2, 8].

In widely used algorithms in the treatment strategy for Budd-Chiari syndrome, gastroesophageal varices and the bleeding thereof have not been considered specific indications for decompressive therapy unless usual pharmacological or endoscopic means for prophylaxis failed to prevent bleeding [1, 8, 9]. In retrospective multicenter studies as well as in prospective follow-up studies, recurrent bleeding from portal hypertension did not appear to be a major problem, even though most patients were receiving long-term anticoagulation therapy. Variceal bleeding accounted for 6 % of the indication for TIPS and 10 % of the indications for liver transplantation in the recent report on the large prospective European cohort study (157 patients followed up for a median of 50 months) [12].

There have been no data reported on the management of acute variceal bleeding in patients with Budd-Chiari syndrome. The particular issue that a marked reduction in portal venous blood flow related to vasoconstrictor therapy could cause portal vein thrombosis has not been addressed. Neither has the issue of early TIPS in patients with advanced Budd-Chiari syndrome or with moderately severe (Child-Pugh B) Budd-Chiari syndrome and active bleeding at endoscopy.

The Interaction of Bleeding with Anticoagulation Therapy

The risk of bleeding in patients with Budd-Chiari syndrome on anticoagulation therapy has been retrospectively evaluated in a single cohort of 94 patients [18]. After a median follow-up of 43 months, 47 patients had 92 major bleeding episodes, 40 of which were related to invasive therapy for BCS. A gastrointestinal origin accounted for 26 of the 52 other episodes, 15 of which were related to portal hypertension. Variceal bleeding occurred in 11 patients, a median of 10 months (range 5–61 months) after the diagnosis of Budd-Chiari syndrome. Current recommendations for prophylaxis of portal hypertensive bleeding had not been followed for three episodes. Five episodes of bleeding from varices or an unidentified source occurred in relation to recent thrombosis of the portal vein in one patient, or early thrombosis of TIPS in three patients, or of a surgical mesentericocaval shunt in one patient. Ascites requiring diuretic therapy at baseline was a risk factor for gastrointestinal bleeding in general and variceal bleeding in particular.

The level of anticoagulation was not specifically evaluated in the group of patients with variceal bleeding [18].

Among 43 consecutive Indian patients with Budd-Chiari syndrome treated only with anticoagulation and supportive medical therapy but no surgical or radiological intervention, 9 had anticoagulation-related complications, including 3 with gastrointestinal bleeding [13]. One patient died from gastrointestinal bleeding.

Another study has addressed the issue of bleeding in patients with and without anticoagulation therapy in a special population of 16 pregnant women afflicted with Budd-Chiari syndrome [19]. Nine of the 16 women had undergone surgical or radiological decompression prior to pregnancy. No variceal bleeding occurred among the 24 pregnancies in these 16 patients, while anticoagulation was administered during 17 pregnancies [19].

Conclusion

While gastroesophageal varices are present at the time of diagnosis in about one half to two thirds of the patients, gastrointestinal bleeding is an uncommon manifestation of Budd-Chiari syndrome. The risk of variceal bleeding appears to be low in patients receiving anticoagulation therapy, when the recommendations for prophylaxis of portal hypertension-related bleeding in cirrhosis are followed, and the decompression of the liver has been achieved to the point of controlling ascites and liver dysfunction. Therefore, with regard to variceal bleeding, it appears that anticoagulation does not play a major deleterious role. By contrast, inappropriate prevention of gastrointestinal bleeding related to portal hypertension, or obstruction of portal vein or therapeutic portosystemic shunts is strongly associated with bleeding or rebleeding. Whether there is an interaction between improper control of portal hypertension and anticoagulation remains to be assessed. The combination of nonselective beta-adrenergic blockers and endoscopic variceal ligation might be of interest to decrease the risk of bleeding. However, the impact of this combination on the overall survival remains unknown. The influence of vasoconstrictor therapy during active bleeding on the risk of portal vein thrombosis is unknown, which justifies keeping its duration short.

Portal Cavernoma

Cirrhosis and malignancy each account for about 25–35 % of extrahepatic portal venous obstruction [20, 21]. Their pathogenesis, manifestations, course, and prognosis differ markedly from those of non-cirrhotic, nonmalignant obstruction, the only form of obstruction which will be considered in this section [1, 8, 9, 22]. From a practical point of view, portal cavernoma is synonymous to long-standing, the so-called chronic extrahepatic portal venous obstruction.

Thrombosis, Prothrombotic Disorders, and Prophylaxis of Thrombotic Events

Portal cavernoma is a well-established consequence of portal vein thrombosis which does not recanalize [23]. However, it is still unclear whether all cases of extrahepatic portal vein obstruction found at the stage of portal cavernoma result from thrombosis [8]. The association with various malformations in children suggests that a congenital anomaly could also be involved [22]. Still, underlying prothrombotic conditions are found in 60–80 % of patients with portal cavernoma [8, 24, 25]. Except for pylephlebitis which is more commonly found in patients with recent portal vein thrombosis, the underlying risk factors for thrombosis do not differ in prevalence or in nature from those identified in acute portal vein thrombosis [8, 24, 25]. Myeloproliferative neoplasms, accounting for approximately 25 % of the cases, rank first among the causes. Several underlying prothrombotic conditions are frequently found to coexist. Surprisingly, a local factor is found in only 25 % of patients investigated early following the development of portal vein thrombosis, and, in such patients, a general prothrombotic condition is often present [8, 23, 25].

There are relatively limited data on the spontaneous risk of recurrent or extensive thrombosis in patients with cavernoma. In the largest retrospective cohort study available [26], 38 thrombotic events developed in 26 out of 119 patients, corresponding to an incidence rate of 5.5 (95 % confidence interval 3.8–7.2) per 100 patient-years. Venous thromboembolic events in the systemic circulation accounted for 13 events, arterial thromboembolism for 5 events, and hepatic, mesenteric, or splenic infarction for 10 events. The two risk factors with independent prognostic value for thrombotic events were an underlying prothrombotic condition (risk ratio 5.3, $P=0.0002$) and anticoagulation therapy (risk ratio 0.39, $P=0.02$) [26]. In another retrospective cohort study on 60 patients with long-standing portal and mesenteric venous thrombosis, all three cases of intestinal resection for mesenteric venous ischemia occurred in patients receiving no anticoagulation therapy [27]. One of the 16 deaths in the latter survey was related to intestinal ischemia [27]. No cases of extrasplanchnic thrombosis were recorded in this study [27]. In another study of seven patients, three episodes of venous thrombosis were observed during an overall observation period of 14 patient-years without anticoagulation therapy [28]. Among 23 other patients followed up for 50 ± 23 months, no thromboembolic event was reported except for one patient dying from stroke [29]. In a survey of 95 patients with portal, splenic, or mesenteric vein thrombosis followed up for a median of 41 months, 10 patients experienced recurrent thromboembolic events while not receiving anticoagulant therapy [30]. In the latter study, underlying myeloproliferative neoplasm was a risk factor for recurrent thromboembolic event [30]. Among 54 patients from a Dutch survey, all with portal vein thrombosis and not receiving anticoagulation, nine venous and one arterial thromboembolic events occurred [31]. In the latter survey, the risk of recurrent thromboembolic event was higher in patients with underlying prothrombotic conditions [31].

The incidence of thrombotic events on anticoagulation therapy has been estimated in five of the six afore-mentioned and discussed surveys, and compared to the incidence in the absence of anticoagulation therapy. In the study by Condat et al., multivariate analysis adjusting for baseline risk factors showed a 70 % reduction in the incidence of thrombotic events when anticoagulation was administered as compared to no anticoagulation [26]. No case of recurrent thromboembolic event was recorded in the study by Orr et al. [27]. Likewise, there was no recurrence during the 64 patient-years spent on anticoagulation in the seven patients studied by Kitchens et al. [28]. There was no recurrent thromboembolic event observed during anticoagulation therapy in the cohort followed by Amitrano et al. [30]. In the survey by Spaander et al., the use of anticoagulation tended to reduce the occurrence of venous thrombotic event (hazard ratio 0.2, $P=0.1$) [31]. These data are highly consistent in suggesting that the risk of recurrent thromboembolic event is increased in patients with strong underlying prothrombotic conditions (e.g., myeloproliferative neoplasm), and that this risk is reduced with anticoagulation therapy. However, the associated level of evidence remains low. Therefore, international expert consensus conferences did not make any recommendations for anticoagulation therapy in patients with portal cavernoma, or only recommended to consider the presence of a strong underlying prothrombotic condition in making a decision for or against prolonged anticoagulation therapy [8, 9, 22].

Bleeding Related to Portal Hypertension and Its Prophylaxis

Recanalization of the portal vein in patients given anticoagulation early in the course of acute thrombosis is about 40 % [23, 32, 33]. Among 25 patients seen at the stage of acute portal vein thrombosis, and in whom portal vein did not recanalize, follow-up endoscopy at a median of 7 months disclosed esophageal varices in 16 (64 %), while no varices were found among the 6 patients with complete or partial recanalization [32]. In two patients from the latter survey, varices had developed as early as 1 month after acute portal vein thrombosis. Four patients experienced a variceal bleeding episode, all with a complete obstruction of the portal vein and while not on anticoagulation therapy [11].

Among patients with portal hypertension admitted to liver centers, the proportion of those that have a portal cavernoma is low. For example, portal cavernoma accounted for 59 of 1,500 patients (4 %) with portal hypertension seen in Padua, Italy, between 1977 and 1989 [29]; for 48 of 602 adult and pediatric patients (7.8 %) in Milan, Italy, in a period of 20 years [34]; and for 15 of 312 patients with esophageal varices (4.8 %) seen in Gothenburg, Sweden, between 1994 and 1999 [35]. The proportion is higher in children as cirrhosis—the competing diagnosis—is uncommon in this age group [36, 37].

Gastrointestinal bleeding as a presenting manifestation for portal cavernoma has decreased with time, in parallel to the development of accurate methods for abdominal vascular imaging [26]. Using these methods, portal cavernoma is now usually

recognized in the follow-up after acute portal vein thrombosis; or following a finding of gastroesophageal varices at endoscopy performed for an unrelated reason, or low platelet counts or enlarged spleen; or fortuitously, during the exploration of unrelated abdominal pain. Gastrointestinal bleeding as a presenting manifestation, as well as the presence of gastroesophageal varices at the time of diagnosis, is difficult to assess because most available surveys included patients with recent and long-standing obstruction and merged patients with cirrhosis and cavernoma with non-cirrhotic nonmalignant disease. In a relatively old study, particular by the fact that the presence of gastroesophageal varices was an inclusion criterion, gastrointestinal bleeding was the presenting manifestation in 16 of 32 patients (50 %) [29]. By contrast, gastrointestinal bleeding was the first manifestation of the disease in only 26 of the 113 patients with portal cavernoma (23 %) seen between 1983 and 1999 [24]. Interestingly, gastrointestinal bleeding was the presenting manifestation in 30 % of the patients seen before 1990, 20 % of those seen between 1990 and 1994, and 17 % of those seen after 1994 [24]. In the same line, in a UK center, gastrointestinal bleeding was the presenting manifestation in 19 (76 %) of 25 patients with chronic portomesenteric venous thrombosis seen before January 2000 versus 13 (37.1 %) of 35 such patients seen after this date [27].

Data allowing for an evaluation of the risk of bleeding during the natural history of portal cavernoma are scarce as (1) in most surveys, acute portal vein thrombosis was not distinguished from portal cavernoma; (2) anticoagulation therapy was administered to some patients; and (3) various treatments were implemented to prevent bleeding. Among 42 patients with routine endoscopy every 1–2 years, 20 had no varices, 8 had small varices, and 14 had medium or large varices at presentation. Patients without varices at presentation did not develop any varices during follow-up; three out of eight patients with small varices progressed to medium or large varices and one of them bled. Five out of 14 patients with medium or large varices had variceal bleeding [30]. Another retrospective survey, where the global incidence of bleeding was 12.5 per 100 patient-year, found that the combination of medium or large varices and the absence of prophylactic therapy for bleeding, and initial manifestations as gastrointestinal bleeding were independent risk factors for bleeding [26]. In the survey by Merkel et al., all 32 patients had esophageal varices at the inception of the study; the risk of gastrointestinal bleeding was 0.23 (95 % confidence interval 0.07–0.34) at 72 months; and the risk of death due to bleeding was 0.14 (95 % confidence interval 0.07–0.30) [29]. In the latter survey, the risk of bleeding was significantly lower in patients with non-cirrhotic portal vein occlusion than in patients with cirrhosis of comparable severity of portal hypertension and of liver dysfunction (hazard ratio 0.35, $P=0.04$) [29]. In a survey from Mumbai, India, on 207 patients presenting with variceal bleeding, 127 patients had more than one bleeding episode, the frequency of which was 0.94 per year [38]. No fixed pattern of frequency of variceal bleeding was identified [38]. The risk of bleeding was increased in patients who experienced a previous bleeding episode [26, 30, 31]. Of 48 patients with non-cirrhotic portal vein thrombosis (17 acute and 31 chronic) seen in Aarhus, Denmark, between 1992 and 2005, 72 % had esophageal varices, 42 % had gastric varices, and 29 %

had gastrointestinal bleeding. Overall 56 % of patients had received anticoagulation. One patient, whose treatment was not provided, died from variceal bleeding [39]. Several surveys identified a previous bleeding episode as a risk factor for subsequent bleeding [26, 30, 31].

Patients with portal cavernoma share with patients with well compensated cirrhosis several features of liver dysfunction which can be precipitated by bleeding, including (1) altered coagulation factor and inhibitor levels [40, 41], which are corrected by surgical restoration of portal perfusion to the liver [42]; (2) relatively frequent, although usually mild and transient, ascites [43]; and (3) rarely, frank hepatic encephalopathy while minimal encephalopathy is surprisingly frequent [44]. All these anomalies can possibly be explained by portosystemic shunting with or without some degree of true hepatic dysfunction.

Good results of surgical portosystemic shunting have been reported in highly selected patients [45–47]. However, in many patients, associated splenic and mesenteric vein thromboses render large, central shunt unfeasible. The long-term benefit of makeshift shunts using collaterals or small portal venous radicles is questionable. Furthermore, the frequent association with an underlying prothrombotic disorder likely increases the risk of thrombosis of surgical shunts. Data on splenectomy and devascularization are limited. Theoretically, splenectomy carries a risk of triggering extensive thrombosis of the portal venous system [48], particularly in patients with portal hypertension [49, 50].

Recent clinical studies have focused on new surgical interventions, and pharmacologic, endoscopic, or radiological procedures to prevent gastrointestinal bleeding. Meso-Rex or mesenteric vein to left-portal vein bypass has mostly been performed in children [51]. It consists of using a venous graft to connect the patent superior mesenteric vein to the patent left-portal vein. Meso-Rex bypass relieves portal hypertension while restoring portal perfusion to the liver. In children, it prevents bleeding from portal hypertension, and corrects decreased levels of coagulation factors and inhibitors, as well as hypersplenism, hyperammonemia, and cognitive disturbances [51]. To the best of the author's knowledge, no data in adults have been reported.

There are no clinical trials available for primary prevention of variceal bleeding. Experiments in the closely related animal model of partial portal vein ligation have shown that beta-adrenergic blocker decreases portal pressure by decreasing portal venous inflow [52, 53]. Beta-adrenergic blocking agents have been found to be independently associated with a decreased rate of bleeding in a retrospective survey [26], and with an improved survival in another survey [27]. As to secondary prevention, it has been shown by randomized clinical trials that endoscopic band ligation is superior to sclerotherapy in children due to a lower risk of rebleeding and complications [54]. Moreover, it has been shown that propranolol is equivalent to band ligation in adults with non-cirrhotic portal hypertension, most of whom had portal cavernoma; the 2-year-rate of rebleeding was 20 % in both treatment groups [55]. The reported experience with TIPS involved a limited number of patients with a short duration of follow-up. At least, it appears to be technically feasible in some patients [56, 57].

The Interaction of Bleeding with Anticoagulation Therapy

The assessment of the influence of anticoagulation therapy on the risk of bleeding has only been performed on retrospective cohorts. This approach has yielded mixed findings which will be discussed in some details thereafter. In the cohort reported by Condat et al., multivariate analysis showed a risk ratio for bleeding associated with anticoagulation therapy 0.77, which was not statistically significant ($P = 0.5$) [26]. Episodes of bleeding occurred only in patients not receiving anticoagulation in the surveys reported by Amitrano et al. [30], and Turnes et al. [32], while Kitchens et al. report that bleeding decreased from 1.2 to 0.2 bleeding episodes per year after institution of anticoagulation therapy in seven patients [28]. In the survey reported by Orr et al. which involved 60 patients of whom 6 had cirrhosis and 4 had malignancy, 2 of 9 (22 %) anticoagulated patients have had recurrent bleeding compared with 16 of 30 (53.3 %) patients not treated with anticoagulation ($P = $NS) [27]. In the latter study, multivariate analysis disclosed that use of coumadin, use of beta-blockers, the absence of ascites, and low bilirubin were independent factors for a longer survival [27]. By contrast, recent data from the Netherlands indicate an increased risk of bleeding (hazard ratio 2.0, $P \leq 0.01$)—although not an increased risk of death—in patients receiving anticoagulation therapy [31]. In the latter study the risk of first bleeding was 33 % (95 % CI 24–41) at 1 year, 43 % at 5 years (95 % CI 33–53), and 46 % (95 % CI 36–56) at 10 years; the overall risk of rebleeding was 46 % (95 % CI 36–56) at 1 year, 63 % (95 % CI 52–74) at 5 years, and 69 % (95 % CI 59–62) at 10 years [31]. These incidence figures appear to be particularly high in this retrospective multicenter study compared to the other surveys, which raises the issue of the application of a strategy for preventing variceal bleeding, an information which was not available [31]. Importantly, all studies concur on the finding that anticoagulation was not associated with an increased severity of bleeding occurring on anticoagulation therapy [26, 28, 31]. No patient died as a result of bleeding on anticoagulation therapy [21, 26, 28, 30–32, 58]. By contrast, several patients receiving no anticoagulation were reported to have died for gastrointestinal bleeding [21, 26].

Conclusion

At present, gastrointestinal bleeding is a presenting manifestation of portal cavernoma in less than 30 % of patients. However, gastroesophageal varices will develop in about 60 % of patients with cavernous transformation of the portal vein following acute portal vein thrombosis. Early anticoagulation appears to be the best preprimary prophylaxis means available as, by preventing long-standing obstruction of the portal vein in 40 % of patients, it efficiently prevents the development of gastroesophageal varices and thus gastrointestinal bleeding. The spontaneous risk of bleeding in patients with established cavernoma is not clearly known as currently available data pertain to patients receiving prophylaxis for bleeding related to portal hypertension and also, for a part of them, long-term anticoagulation. Size of

esophageal varices, the absence of adequate prophylaxis for portal hypertension, and a past bleeding episode related to portal hypertension consistently appear to be risk factors for bleeding or rebleeding. The risk of bleeding during follow-up is 12–33 % in the first year. The annual rate of first bleeding appears to be lower thereafter. Data on nonselective beta-adrenergic blockade and of endoscopic ligation of esophageal varices are in line with those collected in patients with cirrhosis. These last two methods can be recommended for the prevention of the first or recurrent bleeding in patients with cavernoma. In children, uncontrolled clinical studies on meso-Rex shunt after a first gastrointestinal bleeding are encouraging, but the respective place of the meso-Rex shunt and endoscopic band ligation is not known. Data on beta-adrenergic blocking agents in children are lacking. Anticoagulation does not increase the severity of bleeding in patients with cirrhosis and has not been associated with any reported death from gastrointestinal bleeding. The evidence for an increased risk of bleeding with anticoagulation is weak while the data supporting a beneficial effect on the risk of recurrent thrombosis are consistent. Therefore, in patients with a strong underlying prothrombotic condition, once pharmacologic and or endoscopic prevention of bleeding from portal hypertension has been implemented, it is likely that anticoagulation can be used safely. The place for portosystemic shunting is narrow. Portosystemic shunting—be it surgical or radiological—should be considered only in selected patients with refractory bleeding, when the venous anatomy makes technical success most probable.

Idiopathic Non-cirrhotic Portal Hypertension

This underestimated but still rare condition is characterized by (1) portal hypertension; (2) a patent extrahepatic portal vein (at least initially) and venous outflow tract; (3) the absence of cirrhosis or condition known to cause cirrhosis, such as viral hepatitis, alcohol abuse, and diabetes; and (4) the absence of congenital hepatic fibrosis, schistosomiasis, and sarcoidosis [59, 60]. Several types of changes are found at liver biopsy including nodular regenerative hyperplasia, perisinusoidal fibrosis, sinusoidal dilatation, multiplication of vascular channels in the portal tracts, ectopic vessels, and a fibrous obliteration of the small intrahepatic portal vein [60, 61]. The later change is thought to be the main initial lesion but it is still unclear that portal obliteration explains all cases of idiopathic non-cirrhotic portal hypertension [62, 63]. The etiology of the disease remains largely unknown although an association has been suggested with particular conditions, including long-term exposure to certain xenobiotics, immunologic disorders, prothrombotic conditions, infectious conditions, and genetic disorders [59].

By definition, portal hypertension is a major feature of the disease. However, clinical, laboratory, and imaging features of portal hypertension may be lacking in patients with typical liver microscopic changes [61]. Presentation varies according to countries, apparently more due to difference in access to health care than to different natural history. Most patients in India present with gastrointestinal bleeding

[60, 64, 65], whereas in most patients in western countries or Japan the initial manifestation is with hypersplenism [62, 66].

A particular feature in natural history is an extremely high risk of portal vein thrombosis [59, 61, 62]. However, the great majority of patients do not have a strongly prothrombotic, underlying condition. Thus, prophylactic anticoagulation does not seem justified at present. It has been proposed to screen with abdominal imaging for the development of portal vein obstruction at regular intervals and to initiate early anticoagulation when thrombosis is demonstrated [59].

The management of acute variceal bleeding, or the primary and secondary prevention has not been the topic for specific randomized controlled clinical trials. The information available has been recently reviewed [10, 59, 60]. It appears reasonable to apply to these patients the recommendations elaborated for portal hypertension due to cirrhosis [59, 60, 63].

Portal Vein Thrombosis in Patients with Cirrhosis

In cross-sectional studies, a portal vein thrombus is found in about 10–20 % of patients [67, 68]. The prevalence of portal vein thrombosis increases with the severity of liver disease [67, 69]. In most patients, the thrombus only partially occludes the portal vein lumen. Over time, the portal vein thrombus appears and disappears unpredictably in most patients [70]. Portal cavernoma is extremely uncommon [70].

Suggested risk factors with an independent association to the development of portal vein thrombosis include a cirrhosis-associated prothrombotic state, a decreased portal blood flow velocity, and the concurrence of underlying inherited thrombophilia. It is now well recognized that patients with cirrhosis have a marked decrease in coagulation factor levels which is not paralleled by a hypocoagulable state [71, 72]. Actually, there is laboratory evidence for a hypercoagulable state due to an imbalance between coagulation factors (increased factor VIII levels) and inhibitors (decreased protein C levels) [72]. The procoagulable state appears to parallel the severity of liver disease. Furthermore, there is epidemiological evidence for cirrhosis being a moderate risk factor for deep vein thrombosis [71]. Decreased portal blood flow velocity is a well-known feature of portal hypertension and advanced liver disease [73, 74]. A prospective study recently suggested that portal blood flow velocity is a risk factor independent from baseline MELD [75], which is in line with the Virchow's triad for venous thrombosis. Last, the Leiden mutation of prothrombin gene has been suggested to be strongly associated with the development of portal vein thrombosis [69].

The association of portal vein thrombosis with the severity of liver disease has led to the suggestion that impaired portal perfusion could cause a worsening of the liver disease. However, it is very difficult to substantiate this view with the available cross-sectional data [76]. Recent analyses of large databases on patients considered for liver transplantation actually failed to find an association between portal vein thrombosis and a poor outcome prior to liver transplantation [77, 78]. However, a deleterious impact of portal vein thrombosis on post-transplantation outcome has

been shown repeatedly [68, 77, 78]. Still, whatever the causal relationship, there is an unfavorable association between portal vein thrombosis and gastrointestinal bleeding [69, 79, 80].

The possible relationship with severity has stimulated attempts at recanalization of the portal vein with the administration of anticoagulation [79, 81–83]. These uncontrolled study have indicated that anticoagulation is reasonably safe in such patients, and that recanalization can be obtained in about 40 % of patients. However, the impact of recanalization on hard outcome measures remains to be shown. The difficulties in assessing pre- and per-treatment hypocoagulability have been the topic of recent reviews. No fully satisfactory means is currently available [84, 85].

TIPS has also been retrospectively evaluated in patients with portal vein thrombosis. TIPS was found to be feasible when intrahepatic portal vein branches are visible, and that recanalization is observed in the absence of anticoagulation [81, 86, 87]. The latter finding highlights the role of a high flow velocity on the control of the intraportal coagulation processes. However, indication for TIPS in these surveys had mostly been for complications of portal hypertension refractory to medical or endoscopic therapy, not specifically for portal vein thrombosis. No difference was found between the outcome of patients with and without portal vein thrombosis in these patients treated with TIPS. A specific effect in patients with portal vein thrombosis could not be evaluated with these data.

Recently, the results of a recent controlled (but not blinded) study testing prophylaxis of portal vein thrombosis in patients with cirrhosis of intermediate severity (Child-Pugh score 7–10) rose much interest [88]. A course of 48 weeks of enoxaparin, 4,000 IU daily, fully prevented the development of portal vein thrombosis, decreased 2-year-mortality rate, and prevented the development of complications, mainly ascites. The magnitude of the effect on complications was much greater than on portal vein thrombosis. Variceal bleeding occurred in control, 1 of 36 control patients (2.7 %), and 2 of 34 patients on enoxaparin (5.8 %; $P<0.521$). There was also evidence for a decreased bacterial translocation during treatment with enoxaparin [88]. These data suggest that it is possible to prevent the worsening of cirrhosis by administering heparin-based anticoagulation, without increasing bleeding-related morbidity and mortality. As extensive portal and hepatic venous thromboses are found in the liver of patients with advanced liver disease [89, 90], it is tempting to speculate that enoxaparin exerted its beneficial effect by preventing the development of intrahepatic thromboses. Whether this approach could be of value for the prevention of portal hypertension-related bleeding has to be evaluated.

In conclusion, although portal vein thrombosis is linked to the severity of cirrhosis, its role in worsening liver disease is still unclear. Anticoagulation appears to be safe, particularly with regard to gastrointestinal bleeding related to portal hypertension. The extent to which anticoagulation induces recanalization has to be assessed in controlled trials. The impact of portal vein recanalization has to be evaluated. Currently, the situation in which anticoagulation appears to be best grounded is represented by the patient with cirrhosis and portal vein thrombosis, waiting for liver transplantation or who could eventually become a transplant candidate if its disease was to worsen.

By contrast with these yet unconvincing data on anticoagulation for established portal vein thrombosis, data suggest that anticoagulation given before portal vein thrombosis develops might prove efficient in reducing the risk of gastrointestinal bleeding in patients with cirrhosis.

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