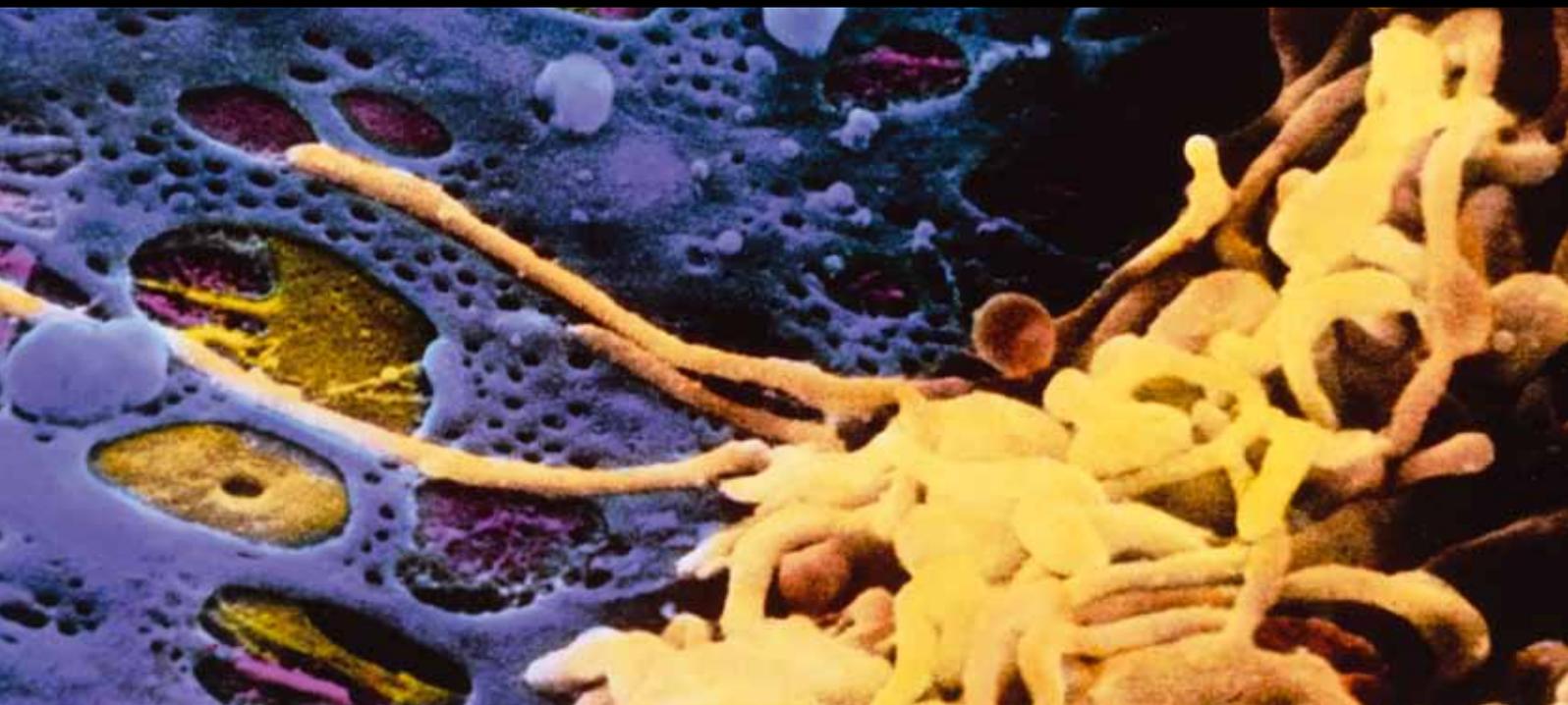


# Esophageal Varices: Pathophysiology, Approach, and Clinical Dilemmas

Guest Editors: Nir Hilzenrat, Marc Bilodeau, and Averell H. Sherker





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International Journal of Hepatology

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## Editorial

# Esophageal Varices: Pathophysiology, Approach, and Clinical Dilemmas

**Nir Hilzenrat<sup>1</sup> and Averell H. Sherker<sup>2</sup>**

<sup>1</sup>McGill University, Montreal, QC, Canada

<sup>2</sup>Liver Diseases Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA

Correspondence should be addressed to Nir Hilzenrat, nir.hilzenrat@mcgill.ca

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Portal hypertension is one of the most significant complications of both acute and chronic liver diseases. It generally develops as a result of an increase in vascular resistance at the prehepatic, intrahepatic, or posthepatic level. An increase in portal blood flow may also contribute. The dominant cause of portal hypertension relates to liver cirrhosis which increases resistance through the hepatic sinusoids. Gastroesophageal varices are the most important clinical manifestation of this syndrome and are associated with a high risk of upper gastrointestinal hemorrhage and its attendant high mortality.

This special issue includes nine evidence-based reviews. They discuss the pathophysiology of portal hypertension as well as its clinical manifestations and management. Selected topics and controversies related to esophageal varices are covered, including noninvasive diagnostic methods, bleeding prophylaxis in adults and children, rescue treatments, and the clinical dilemma of portal vein thrombosis.

H. Maruyama and O. Yokosuka review the current concepts of the pathophysiology of portal hypertension and esophageal varices. Portal hypertension is initially caused by distortion of the hepatic vascular bed, which in turn leads to increased resistance to portal blood flow. This phenomenon is associated with intrahepatic endothelial dysfunction with a resultant imbalance between vasodilators such as nitric oxide and prostaglandins vasoconstrictors including endothelin. An important consequence of increased resistance to portal blood flow is splanchnic vasodilatation with consequent sodium and water retention. As a result of the plasma's expansion, and the reduction in peripheral resistance, a hydrodynamic circulation develops. Consequently, there is a

significant increase in the blood flow through the portal vein which further contributes to portal hypertension. Esophageal varices appear and may bleed when the HVPg exceeds 12 mmHg.

A comprehensive review of the clinical manifestations of portal hypertension is presented by S. A. Al-Busafi et al. Portal hypertension is a common clinical syndrome defined as the elevation of hepatic venous pressure gradient (HVPG) above 5 mmHg. Its gastrointestinal manifestations include the development of esophageal varices, gastric varices, and intestinal vasculopathy. Approximately 5–15% of cirrhotics develop esophageal varices annually. The majority of patients with cirrhosis are expected to develop this condition over their lifetime. Beyond its gastrointestinal effects, portal hypertension may also affect other vital organs resulting in extrahepatic manifestations.

Y.-I. Chen and P. Ghali present an overview of strategies to prevent and manage portal hypertension. The one-year rate of first variceal hemorrhage is 5% for small varices and 15% for large varices. Six-week mortality rate following an episode of bleeding varies between 15 and 20%. Clearly, a strategy of prophylaxis to prevent the first episode of bleeding may reduce morbidity and mortality. In this respect, nonselective beta blockers and new types of beta blockers play a major role. The overall approach and the current pharmacological therapy of acute hemorrhage and of recurrent bleeding (i.e., secondary prophylaxis) are based on understanding the pathophysiology of esophageal varices.

Early diagnosis of esophageal varices prior to the first episode of bleeding is essential. Studies of primary prophylaxis clearly show that the risk of first variceal haemorrhage

can be reduced significantly. Upper GI endoscopy remains the gold standard for screening, but this test is not without its own limitations. K. Rye et al. review the utility of noninvasive tests to predict esophageal varices. Unfortunately, current clinical, biochemical, and radiological parameters are not accurate enough to detect varices without a screening endoscopy, but assessment of systemic hemodynamics and other serum markers may hold promise for the future.

Variceal rupture is governed by Laplace's law. Increased wall tension is the end result of increased intravariceal pressure, increased diameter of the varices, and reduced wall thickness. The variceal wall thickness can be evaluated visually by the presence of red wale markings. These markings reflect areas where the wall is especially thin. Variceal rupture often occurs at the level of the gastroesophageal junction where the varices are very superficial and thus have thinner walls. S. A. Al-Busafi et al. discuss the role of endoscopic management of esophageal varices. They emphasized the fact that gastroscopy allows direct visualization and is an excellent tool to assess the size and the presence of high risk stigmata of bleeding. A debate exists as to whether a pharmacologic or an endoscopic approach is the best method of primary prophylaxis. It was shown that both modalities are effective in minimizing the risk of a first episode of bleeding in patients with cirrhosis and large esophageal varices, independently of the presence of red signs. However, the endoscopic approach is the treatment of choice whenever the patient is unable to tolerate beta blockers. Acute variceal bleeding in patients with cirrhosis indicates decompensation and a high risk of death. Initial treatment for these patients includes volume resuscitation and administration of vasoactive drugs and antibiotics. Emergency endoscopic variceal ligation, one of the cornerstones of management, should be performed within the first 12 hours of hospital admission.

G. Pomier-Layrargues et al. highlight the role of transjugular intrahepatic portosystemic shunt (TIPS) in the treatment of acute esophageal varices bleeding. The clinical trials indicate that the TIPS procedure is not a first line therapy for variceal bleeding but can be used when medical and endoscopic treatments fail, either in the acute situation or to prevent variceal rebleeding. However, careful selection of patients is mandatory before the TIPS procedure. Clinical followup is essential to detect and treat complications that may result from TIPS stenosis, which can be minimized by using covered stents. Followup is also required to monitor for worsening portosystemic encephalopathy. In severe cases of encephalopathy, reduction or occlusion of the shunt may be warranted.

The current first line pharmacologic and endoscopic therapies fail to control bleeding in approximately 10–15% of patients. Rescue therapies, which include balloon tamponade or TIPS, have many limitations and are contraindicated in some cases. A novel, emerging therapy is reviewed by F. Maufa and F. H. Al-Kawas. Placement of a fully covered self-expandable metallic stent can be used to control bleeding in cases of refractory esophageal hemorrhage. The removable stent can be left in place for as long as two weeks, allowing for improvement in liver function while a more definitive treatment can be planned semielectively.

Portal hypertension in children represents a particular challenge in both diagnosis and management. A. Costaguta and F. Alvarez describe the progress that has been achieved recently in the treatment of children with portal hypertension. Two main factors influence therapeutic decisions: the age of the patient and the etiology of the liver disease. In this special issue, one can find a summary of the current knowledge and an expert opinion on the subject.

Finally, nonneoplastic portal vein thrombosis (PVT) can be found in up to 25% of individuals with liver cirrhosis. The major risk factor of having PVT is severe liver disease and portal hypertension. Recently, it was found that procoagulant imbalance in individuals with advanced liver disease contributes to the development of PVT. The clinical impact of PVT on liver function is not clear. Nevertheless, it is a predictive factor for mortality among cirrhotics, independent of MELD score. PVT may be the cause of various life-threatening conditions. It increases portal hypertension and the risk of variceal bleeding. It may also extend into the superior mesenteric vein causing intestinal ischemia. The optimal management of PVT in individuals with cirrhosis is currently not addressed in any consensus publication or practice guidelines. G. Huard and M. Bilodeau explore the different aspects of PVT management including the potential risks and benefits of anticoagulation.

This special issue provides an excellent overview of one of the more complicated topics in the field of liver disease. It covers current concepts of the clinical and pathophysiological aspects of portal hypertension, management of the condition, along with emerging diagnostic and therapeutic modalities, and clinical controversies. We would like to congratulate the authors for their superb scientific manuscripts.

*Nir Hilzenrat  
Averell H. Sherker*

## Review Article

# Etiology and Management of Hemorrhagic Complications of Portal Hypertension in Children

Alejandro Costaguta<sup>1</sup> and Fernando Alvarez<sup>2</sup>

<sup>1</sup>Unidad de Hígado y Trasplante Hepático, Sanatorio de Niños, Alvear 863, Santa Fe, Rosario 2000, Argentina

<sup>2</sup>Service de Gastroentérologie, Hépatologie et Nutrition, CHU Sainte-Justine, Université de Montréal, 3175 Côte Sainte-Catherine, Montréal, QC, Canada H3T 1C5

Correspondence should be addressed to Fernando Alvarez, fernando.alvarez@umontreal.ca

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Portal hypertension in children represents a particular diagnostic and management challenge for several reasons: (1) treatment outcomes should be evaluated in relationship with a long-life expectancy, (2) pediatric patients with portal hypertension constitute an heterogeneous population, both in terms of individual characteristics and diversity of liver diseases; making comparison between treatment outcomes very difficult, (3) application of techniques and procedures developed in adult patients (v.gr. TIPS) face size limitations in small children, and (4) absence of data from well-controlled trials in children forces pediatric specialists to adapt results obtained from adult cohorts suffering from diseases such as HCV and alcoholic cirrhosis. Despite those limitations, substantial progress in the treatment of children with portal hypertension has been achieved in recent years, with better outcomes and survival. Two main factors influence our therapeutic decision: age of the patient and etiology of the liver disease. Therefore, diagnosis and treatment of complications of portal hypertension in children need to be described taking such factors into consideration. This paper summarizes current knowledge and expert opinion.

## 1. Presinusoidal Portal Hypertension

*1.1. Portal Vein Obstruction.* Portal obstruction is the single most common etiology of portal hypertension in children, representing roughly 50% of all cases in the majority of series. The causes of portal vein obstruction fall into one of following categories: perinatal events (umbilical catheterization, omphalitis, and dehydration), congenital malformations outside the portal vein (Abernethy malformation), thrombophilic states (deficiency of protein-C, S or antithrombin-III, etc.), tumors, abdominal infections, and a category where the etiology is unknown [1, 2].

Portal obstruction in children is usually detected early in the first decade, because of splenomegaly, gastrointestinal bleeding, or both [3]. Development of esophageal varices is almost universal, and the actuarial risk of bleeding reaches 76% at 24 years of age. Probability of bleeding is directly correlated with the size of varices as seen on endoscopy, from the absence of bleeding episode in children without varices

or with grade I varices, to 85% prevalence of bleeding in patients with grade II or III varices, as reported by Lykavieris et al. [4]. Of note, this study showed that varices tended to increase in size over the years instead of disappearing, defying the classical concept of spontaneous improvement as children grow-up.

Variceal bleeding is generally well tolerated, owing to normal function of the liver; however, the main concern in the management is to reduce the recurrence of episodes. Endoscopic therapy works by physical obliteration of esophageal varices and has shown excellent results, with a 90% rate of success in the long-term control of bleeding [5]. It usually represents the first approach due to its relative simplicity, low frequency of immediate complications, and widespread availability. The high rate of success has led to ample use of this technique; however, an increase of long-term complications is usually observed, as bleeding from ectopic varices, low-grade encephalopathy, hepatopulmonary syndromes, further development of hypersplenism,

and cholestasis secondary to portal cholangiopathy. Particularly challenging is the management of cholestasis; this syndrome has been described in 6% of patients with portal vein obstruction, especially after long-term followup [6, 7], and it is the consequence of dilated peribiliary venous plexus (cavernoma) in the wall of biliary ducts (Figure 1). Affected patients exhibit high levels of GGT and Bilirubin, with dilated bile ducts (mainly intrahepatic) as seen on the abdominal ultrasound. Biopsy samples show different degrees of fibrosis and even biliary type of cirrhosis, with a pattern indistinguishably from primary sclerosing cholangitis in some cases [6].

Complete resolution can be achieved with surgical decompression of the portal system by means of a portosystemic or a meso-Rex shunts. In rare cases persistent biliary strictures remain present after shunt surgery. Probably ischemic in nature, they can be resolved by hepaticojejunostomy [7].

**1.2. Congenital Hepatic Fibrosis.** Congenital hepatic fibrosis (CHF) is part of a spectrum of fibropolycystic diseases, in which the pathological hallmark is the presence of *ductal plate malformation* [8]. It combines biliary dysplasia, peribiliary fibrosis, and renal polycystic disease in different patterns, giving rise to a wide diversity of clinical manifestations observed throughout the years. Two different forms have been described in association with renal disease: autosomal recessive (ARPKD) and dominant (ADPKD) polycystic kidney diseases [9].

In ARPKD, clinical signs of renal disease can be observed during the first years, appear later, or remain subclinical. Findings of portal hypertension become evident, generally in the first years of life, usually in the form of variceal bleeding and hypersplenism. It has been estimated that 25% of affected individuals develop clinically significant portal hypertension, with a trend toward increased frequency with increasing age [10]. Interestingly, children with portal hypertension were younger than the mean age of the whole cohort, suggesting that a particular subset of patients is at risk of developing this complication, probably related to specific still unknown genetic or environmental factors.

ADPKD patients, in contrast with ARPKD, tend to present later in life with progressive renal disease and less liver involvement. However, because variceal bleeding can occur as early as age 4, screening relatives of the index case (most commonly an adult with multiple renal cysts) by regular ultrasounds have been recently advocated [11].

CHF has also been reported as part of other rare syndromes, such as nephronophthisis (with end-stage renal disease within 5 to 10 years), Jeune syndrome (lung and thoracic hypoplasia), Meckel-Gruber syndrome (encephalocele and polydactyly), Ivemark syndrome (interstitial fibrosis leading to renal failure), chronic diarrhea related to enterocolitis cystic superficialis and intestinal lymphangiectasia, and others. In all cases, accompanying liver findings include ductal plate malformation, fibrosis, and biliary cysts in different combinations [12].

Patients with congenital hepatic fibrosis characteristically have well-preserved liver function; they behave as those with



FIGURE 1: Portal cholangiopathy: this 18-year-old-boy presented with fever and jaundice. He has been treated with endoscopic sclerosis of esophageal varices from the age of six, because of portal hypertension secondary to extrahepatic portal vein obstruction. Cholangio-MRI shows dilated intrahepatic biliary tree, proximal to the level of stenosis (circle). GB: gallbladder.

portal vein obstruction, with regard to the risk and tolerance to bleeding. Moreover, cavernomatous transformation of the portal vein and abnormal intrahepatic branching have been described in CHF patients, suggesting that anomalies in the development of portal veins are part of the spectrum of liver disease in this condition [13, 14].

Given the relatively benign liver disease, management recommendations for children with CHF-related portal hypertension are based on endoscopic eradication of varices. However, the frequent need for kidney transplantation in children with ARPKD leads to perform a surgical portosystemic shunt before the transplant surgery. Successful shunt facilitates abdominal surgery and avoids varices bleeding that could represent a risk for the transplanted organ. For the rare patients with repeated acute or chronic cholangitis, who develop cirrhosis, or for those with pulmonary complications, liver transplantation is a potential therapeutic option. Decision about when (and if) to combine it with kidney transplantation should be considered on a case-by-case evaluation [15].

## 2. Cholestatic Cirrhosis

**2.1. Biliary Atresia.** This disease affects 1 in 15000 to 1 in 20000 newborns and constitutes the main indication for liver transplantation in children. Current treatment strategy includes the Kasai portoenterostomy operation, followed by liver transplantation in cases of its failure or later complications from cirrhosis [16]. Children with biliary atresia tend to develop varices very early, with an estimated risk of bleeding of 15% before the age of two [17]. When associated with high bilirubin levels, it portends a poor prognosis, and constitutes an indication to proceed to transplantation as soon as possible, owing to the more than tenfold rise in the risk of death when conjugated bilirubin levels are over 10 mg% [18]. Even in anicteric patients, there is a considerable risk of bleeding, highlighting their tendency to suffer from severe

portal hypertension, probably related to the intense fibrosis as is observed at the time of portoenterostomy, and the diffuse compromise of intrahepatic portal vein described in some [14]. Cholangitis, a frequent complication after portoenterostomy, can be responsible for thrombophlebitis of the portal system, accelerating the development of portal hypertension [19].

Bleeding can be predicted in patients with large varices, associated red signs, presence of gastric varices, and portal hypertensive gastropathy (Figure 2) [17]. Recent data supports the implementation of prophylactic sclerotherapy or banding to prevent the first hemorrhage. Endoscopy screening can be suggested to begin around 12 months of age. Sclerotherapy would be preferred over rubber band ligation owing to size constraints faced in little children [20].

**2.2. Cystic Fibrosis.** Approximately 5% of cystic fibrosis patients develop liver cirrhosis before adolescence [21].

Like other cholestatic type of cirrhosis, it is characterized by a high degree of portal hypertension, with preserved synthetic function for many years [22, 23]. As the management of lung disease continues to improve, liver disease is becoming a major determinant of the outcome, being the third most common cause of death [24]. It has been estimated that nearly 60% of cirrhotic patients experienced an episode of variceal bleeding before the second decade of life [23], contributing to the 10 to 20% of deaths in the cystic fibrosis group as a whole [24]. Data coming from recent cohort studies show that liver disease in Cystic Fibrosis patients poses a special threat to their wellbeing and survival. This is not only related to the complications of cirrhosis itself; affected children tend to have higher Shwachman scores and worse pulmonary function suggesting a synergistic effect between liver and lung disease [22, 25]. In fact, improvement in the severity of respiratory disease is well documented after liver transplantation in many of those patients [24, 26]. Altogether, approaching a child suffering from variceal bleeding in the context of Cystic Fibrosis should be tailored to each specific case. Endoscopic treatment should be offered to all, being especially useful in the context of acute hemorrhage. However, concern remains over the long-term endoscopic treatment due to the need for multiple anesthetics procedures, and the possible development of pulmonary complications from portal hypertension itself. In patients with relatively well-preserved liver and lung functions, a selective portocaval shunt (or a TIPS, when feasible) could offer many years of benefit without compromising the outcome [23, 27]. Patients with advanced liver disease, or severe and refractory bleeding, with good pulmonary function are probably best managed with liver transplantation [24, 26, 28]. Results of combined liver-lung transplantation are currently not encouraging; hence waiting for advanced lung disease before deciding to go for liver transplantation does not seem to be advisable [29].

### 3. Other Etiologies of Portal Hypertension

**3.1. Noncirrhotic Portal Hypertension (Hepatoportal Sclerosis).** This presinusoidal type of portal hypertension is produced



(a) Grade 1 esophageal varices without red signs: this low-risk type of varices can be managed conservatively



(b) Grade 3 esophageal varices with red signs: the high rate of bleeding associated could be best managed with prophylactic eradication

FIGURE 2: Different types of esophageal varices on endoscopic examination.

by intimal thickening of small intrahepatic portal vein radicles. The clinical picture resembles that of prehepatic portal vein obstruction but with a patent (an even, dilated) portal vein on ultrasound. Well-tolerated variceal bleeding and hypersplenism have been reported in this syndrome mainly described in Asian patients [30]. Recent reports coming from western-country children surviving from acute leukemia treated with 6-thioguanin highlights the alleged toxin exposure as one of the possible causes of the endothelial damage [31]. Management of these patients follows the same rules applied for portal vein obstruction.

**3.2. Postnecrotic Cirrhosis.** Chronic hepatitis associated to HBV or HCV infection can rarely present in the first two decades of life with a picture of portal hypertension secondary to cirrhosis. Management is not different from that in adult patients. Children exhibit better responses rates to antiviral treatment; thereby there is better control of complications, including those of cirrhosis [32–34].

*Autoimmune hepatitis* is the most common cause of post-necrotic cirrhosis in children. Appropriate treatment with immunosuppressive drugs usually results in control and regression of fibrosis in most patients. A small percentage, however, progresses to decompensated cirrhosis and hemorrhagic complications; these should be managed in a staggered manner according to the medium-term prognosis of

the disease, from endoscopic treatment to liver transplantation in end-stage patients [35].

*Alpha-1-antitrypsin deficiency* produces a picture combining findings of cholestatic and postnecrotic cirrhosis. It is the most common indication for liver transplantation from metabolic diseases in the Western hemisphere. Although some improvement of liver function tests has been reported with the use of ursodeoxycholic acid, at the present, there is no effective treatment for this condition, and management of affected patients is restricted to the complications of ongoing cirrhosis, using the same principles described for other etiologies [36].

*Budd-Chiari Syndrome* encompasses a series of different causes producing obstruction to the hepatic venous outflow. These patients tend to present with hepatomegaly and ascitis rather than with variceal hemorrhage, but those developing secondary cirrhosis can experience bleeding from esophageal varices. Management is very complex, strongly influenced by the clinical picture (acute versus chronic), etiology, and extent of the liver damage. In contrast with portal vein obstruction, most Budd-Chiari patients have an associated thrombophilic state that has to be accurately investigated and treated [37].

## 4. Treatment

*4.1. Prevention of the First Bleed (Primary Prophylaxis).* Avoiding the morbidity and mortality associated with the first bleed from esophageal varices is the rationale behind primary prophylaxis. Clear recommendations exist for the adult population, but unfortunately this is not the case for pediatric patients [38]. Application of such strategy should comply with two premises: correct identification of the population “at risk” and availability of an effective treatment. In spite of many efforts, achieving the first goal has been elusive, owing to the heterogeneity of the population with portal hypertension in pediatric ages [39]. Stratifying patients at risk according to specific etiologies could be the best way to manage this problem [17]. Regarding the second goal, the absence of controlled randomized trials in primary prophylaxis of esophageal varices bleeding in children makes any recommendation problematic and debatable. Low number of patients and difficulties in recruitment are major obstacles to the realization of such studies, as seen with the use of propranolol in children, which is in strong contrast to the adult population. A group of experts analyzed possibilities on primary prophylaxis of variceal hemorrhage in children, concluding that future research should focus on the natural history, diagnosis of varices, prediction of variceal bleeding, and explore therapeutic efficacy of different protocols [40].

Currently, it remains intuitive to offer endoscopic obliteration to patients with high-risk varices who had never bled, preferably by band ligation. Endoscopic examination should be only offered to patients when decision to proceed with sclerotherapy or banding has already been taken in advance [5, 20].

Data in children with cirrhosis secondary to biliary atresia showed that esophageal varices developed very early in

life in 70% of them. In addition, endoscopic signs indicating a high risk of mediate bleeding were found in 30% of those with esophageal varices [20]. Another recent study, on a similar population, showed that grade II-III varices developed with similar frequency after failed and successful portoenterostomy, but, following failed portoenterostomy, esophageal varices were encountered significantly earlier [41]. The authors recommended that after failed portoenterostomy surveillance should start early, for example, at six months of age [41].

There are different approaches in the care of children at risk for esophageal varices bleeding among pediatric gastroenterologists, most of them based on personal preferences and local expertise rather than strong evidence. In addition, attitudes from parents could be different from those of physicians; a high percentage of them would accept an endoscopy to be carried out in their children if a prophylactic treatment can avoid bleeding or even to establish the current risk of bleeding in the absence of treatment [42].

*4.2. Acute Bleeding.* Acute bleeding is the most feared complication of portal hypertension, with an associated mortality up to 20%, mainly in patients with affected liver function [43]. As a consequence, focus on treatment has been directed to the control of hemorrhagic episodes, reaching a rate of success higher than 90% in recent years.

Volume resuscitation initiated without delay, should restore hemoglobin levels to around 8 g%, and insure good perfusion of vital organs with plasma expanders. Overzealous use of volume/plasma expanders should be avoided, however, because of the theoretical risk of rebound portal hypertension and rebleeding [38].

Antibiotics directed at the intestinal flora should be part of the treatment from the beginning [38], as well as vasoactive drugs, preferably by the intravenous route. Among many drugs tested in adult patients, octreotide has been the most widely used in children, at a dose of 1-2 ug/Kg by bolus over 20 minutes, followed by continuous infusion at 2 ug/Kg/h, maintained for 2 to 5 days [44]. Its use in this setting has been advocated to promote easier and safer endoscopic procedures [20].

Once stabilized, patients should be treated by direct approach of the varices, either with band ligation or sclerosant injection. Both treatments are highly effective in controlling the acute episode, and the choice of one particular method depends on the local expertise and other technical issues. In a general sense, endoscopic variceal ligation is preferred in most cases, owing to its simplicity and lower rate of complications, but sclerotherapy is probably easier to implement during active bleeding, and is the best option in small children [45, 46]. Ideally, the operator should master both techniques and have all appropriate tools available during the procedure.

Despite the high rate of success achieved with these approaches: in 5 to 10% of cases bleeding cannot be controlled, and rescue therapy is needed, usually after the failure of a second attempt by endoscopy. This rescue therapy involves a surgical option, or a radiological approach (TIPS),

TABLE 1: Common causes of portal hypertension in children and suggested management.

Cause	Treatment	Comment
Portal vein obstruction	(1) Endoscopic	Endoscopic treatment consists on elastic banding or sclerotherapy
	(2) Meso-Rex shunt	
	(3) DSR or mesocaval shunt	
Biliary atresia	(1) Endoscopic	Screening at age of 1, prophylaxis in high-risk varices
	(2) Liver transplantation	
Cystic fibrosis	(1) Endoscopic	Need repetitive anesthetics
	(2) DSR or meso-caval shunt	Risk of pulmonary complications and worsening encephalopathy
	(3) Liver transplantation	When good respiratory function
Congenital hepatic fibrosis	(1) Endoscopic	When recurrent cholangitis (need to consider liver and kidney transplantation)
	(2) DSR or meso-caval shunt	
	(3) Liver transplantation	
Other cirrhosis	(1) Endoscopic	If good liver function
	(2) DSR or meso-caval shunt	
	(3) Liver transplantation	In end-stage liver disease

DSR: distal spleno-renal shunt.

when feasible. Once again, both procedures are equally effective, but when used in an emergency scenario their results are less satisfactory [47]. TIPS has the advantage of avoiding a laparotomy, but its availability is limited to specialized services and is not suitable for small children, especially in cases of portal vein obstruction or biliary atresia, which are the main causes of variceal hemorrhage among pediatric patients [38]. The choice of the surgical technique, on the other hand, depends on the medium-term prognosis of the disease. Shunting procedures are preferred in patients with relatively well-preserved liver function, like those with portal vein obstruction, congenital hepatic fibrosis, or compensated cirrhosis. Liver transplantation needs to be considered for children with more advanced disease.

**4.3. Prevention of Rebleeding (Secondary Prophylaxis).** Once the first bleeding has occurred, there is a substantial risk for rebleeding in the next years; consequently, eradication of esophageal varices becomes a logical goal. Endoscopic variceal ligation and sclerotherapy have been reported to be equally successful in achieving this. Variceal ligation is usually preferred because of its reported simplicity, lesser number of sessions needed, and a safer profile when compared to sclerotherapy [45, 46]. Both techniques are complementary and have been used even in primary prophylaxis with good results [5, 20].

An observational study in children with portal hypertension, of several different etiologies, showed a benefit of secondary prophylaxis in avoiding esophageal varices bleeding. In this study, the use of propranolol did not affect results of endoscopic prophylaxis [48]. In contrast, a large study including mainly adolescents did not find

differences between propranolol and endoscopic ligation in the recurrence of bleeding [49].

Longer followup of endoscopic treatments is available, showing recurrence of esophageal varices in 40% of the patients, with a tendency to worsening of gastric varices, portal hypertensive gastropathy, and rising incidence of ectopic varices, all of them representing a more difficult problem to solve [50]. Progression of the spleen size and late incidence of complications like portal cholangiopathy in patients with portal obstruction, formerly considered a rare entity, affect children quality of life. Moreover, for these complications endoscopic treatments are clearly unsuitable [51]. In those cases, or when hemorrhagic episodes are refractory to other treatments, surgery becomes the only option [52].

Shunt procedures could be classified as total, partial, and selective. Total portosystemic shunts are those more than 10 mm in diameter, constructed between the main veins of the portal system and the inferior vena cava. They provide excellent control of hemorrhages and ascitis, but at the high cost of encephalopathy, and are rarely used in children. Partial shunts comprises portocaval or mesocaval anastomoses of 8 mm in diameter or less, allowing part of the portal flow to reach the liver sinusoids, and thus reducing the risk of systemic complications without losing efficacy for the prevention of further bleeding. This type of shunts has been widely used in children employing the internal jugular vein as a graft, with excellent results [53, 54]. Selective shunts are constructed by the anastomoses of the splenic vein to the left renal vein, thereby decompressing gastroesophageal varices through the short gastric veins (distal splenorenal shunt), and maintaining portal perfusion to the liver. Spleno-renal shunts achieve good hemorrhagic control and reduce systemic complications.

Surgical shunts have gained renewed interest in the management of portal hypertension in children with good liver function, in view of better results obtained with the refinement of surgical techniques driven by the development of liver transplantation programs, and the emergence of nonhemorrhagic complications after successful eradication of esophageal varices.

The mesenteric-left portal vein bypass (Rex shunt) is constructed between the superior mesenteric vein and the recessus of Rex at the level of intrahepatic left branch of portal vein. Originally developed to treat patients who have portal vein thrombosis after liver transplantation, it was extended immediately to the treatment of children with extrahepatic portal vein obstruction, allowing them for the first time to reach a real “cure” for their disease. In fact, when successful, it can restore the normal flow to the liver with normalization of hematological tests [55]. Availability of this technique is promoting a change of paradigm in the treatment of portal vein obstruction, towards an early indication of surgery, before progressive fibrosis of the main portal vein branches precludes the feasibility of such anastomoses [56]. The percentage of children with portal obstruction who can benefit for a meso-Rex shunt is still unknown.

Recent data coming from pediatric series, albeit small in number of patients, have reproduced the rates of success obtained in adult patients, making TIPS a good option even in small children and expanding indications to postransplant portal hypertension, and children with portal vein obstruction with a favorable anatomy [57]. Future studies will clarify the role of this therapy in the management of pediatric portal hypertension [58].

## 5. Summary

Treatment of hemorrhagic complications from portal hypertension in children has its own specificities because of the different etiologies involved, and the natural history of these disorders compared to adults (Table 1). Size constraints can also be anticipated in smaller patients. Despite that, considerable progress has been achieved in the last years, mainly derived from better control of bleeding from esophageal varices. Longer followup, however, uncovers new complications for which endoscopic treatment is inappropriate, promoting a renewed interest on surgical approaches. As a general principle, management of portal hypertension in children rests on two main characteristics: the etiology of the portal hypertension and the age of the patient.

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## Review Article

# Clinical Manifestations of Portal Hypertension

Said A. Al-Busafi,<sup>1,2</sup> Julia McNabb-Baltar,<sup>2</sup> Amanda Farag,<sup>3</sup> and Nir Hilzenrat<sup>4</sup>

<sup>1</sup> Department of Medicine, College of Medicine and Health Sciences, Sultan Qaboos University, P.O. Box 35, 123 Muscat, Oman

<sup>2</sup> Department of Gastroenterology, Royal Victoria Hospital, McGill University Health Center, Montreal, QC, Canada H3A 1A1

<sup>3</sup> Department of Medicine, Royal Victoria Hospital, McGill University Health Center, Montreal, QC, Canada H3A 1A1

<sup>4</sup> Department of Gastroenterology, Jewish General Hospital, McGill University, Montreal, QC, Canada

Correspondence should be addressed to Said A. Al-Busafi, busafis@squ.edu.om

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The portal hypertension is responsible for many of the manifestations of liver cirrhosis. Some of these complications are the direct consequences of portal hypertension, such as gastrointestinal bleeding from ruptured gastroesophageal varices and from portal hypertensive gastropathy and colopathy, ascites and hepatorenal syndrome, and hypersplenism. In other complications, portal hypertension plays a key role, although it is not the only pathophysiological factor in their development. These include spontaneous bacterial peritonitis, hepatic encephalopathy, cirrhotic cardiomyopathy, hepatopulmonary syndrome, and portopulmonary hypertension.

## 1. Introduction

Portal hypertension (PH) is a common clinical syndrome defined as the elevation of hepatic venous pressure gradient (HVPG) above 5 mm Hg. PH is caused by a combination of two simultaneous occurring hemodynamic processes: (1) increased intrahepatic resistance to passage of blood flow through the liver due to cirrhosis and (2) increased splanchnic blood flow secondary to vasodilatation within the splanchnic vascular bed. PH can be due to many different causes at prehepatic, intrahepatic, and posthepatic sites (Table 1). Cirrhosis of the liver accounts for approximately 90% of cases of PH in Western countries.

The importance of PH is defined by the frequency and severity of its complications including variceal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome, which represent the leading causes of death and of liver transplantation in patients with cirrhosis. PH is considered to be clinically significant when HVPG exceeds 10 to 12 mm Hg, since this is the threshold for the clinical complications of PH to appear [1]. Proper diagnosis and management of these complications are vital to improving quality of

life and patients' survival. This paper will review the multi-systemic manifestations of PH in cirrhosis.

## 2. Gastrointestinal Manifestations

**2.1. Gastroesophageal (GE) Varices.** Approximately 5–15% of cirrhotics per year develop varices, and it is estimated that the majority of patients with cirrhosis will develop GE varices over their lifetime. The presence of GE varices correlates with the severity of liver disease; while only 40% of child A patients have varices, they are present in 85% of child C patients (Table 2) [2].

Collaterals usually exist between the portal venous system and the systemic veins. The resistance in the portal vessels is normally lower than in the collateral circulation, and so blood flows from the systemic bed into the portal bed. However, when PH develops, the portal pressure is higher than systemic venous pressure, and this leads to reversal of flow in these collaterals. In addition, the collateral circulatory bed also develops through angiogenesis and the development of new blood vessels in an attempt to decompress the portal

TABLE 1: Causes of portal hypertension (PH).

Prehepatic PH (normal wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) with normal hepatic venous pressure gradient (HVPG))
Portal vein thrombosis
Splenic vein thrombosis
Congestive splenomegaly (Banti's syndrome)
Arteriovenous fistula
Hepatic PH (increased WHVP, normal FHVP, and increased HVPG)
Presinusoidal
Schistosomiasis
Congenital hepatic fibrosis
Sinusoidal
Cirrhosis—many causes
Alcoholic hepatitis
Nodular regenerative hyperplasia
Polycystic liver disease
Postsinusoidal
Sinusoidal obstructive syndrome
Budd-Chiari syndrome
Posthepatic PH (increased WHVP and FHVP and normal HVPG)
Inferior vena cava webs, thrombosis
Cardiac causes (restrictive cardiomyopathy, constrictive pericarditis, and congestive heart failure)
Pulmonary hypertension

circulation [3]. The areas where major collaterals occur between the portal and systemic venous system are shown in Table 3. Unfortunately these collaterals are insufficient to decompress the PH, leading to complications including variceal bleeding.

GE area is the main site of formation of varices [4]. Esophageal varices (EV) form when the HVPG exceeds 10 mm Hg [5]. In the lower 2 to 3 cm of the esophagus, the varices in the submucosa are very superficial and thus have thinner wall. In addition, these varices do not communicate with the periesophageal veins and therefore cannot easily be decompressed. These are the reasons why EV bleeds only at this site.

Over the last decade, most practice guidelines recommend to screen known cirrhotics with endoscopy to look for GE varices. Varices should be suspected in all patients with stigmata of chronic liver disease such as spider nevi, jaundice, palmar erythema, splenomegaly, ascites, encephalopathy, and caput medusae. EV are graded as small (<5 mm) and large (>5 mm), where 5 mm is roughly the size of an open biopsy forceps [6].

The rate of progression of small EV to large is 8% per year [2]. Decompensated cirrhosis (child B or C), presence of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface), and alcoholic cirrhosis at the time of baseline endoscopy are the main factors associated with the progression from small to large EV

TABLE 2: Child-Pugh-Turcotte (CPT) Classification of the Severity of Cirrhosis.

Parameter	Points assigned		
	1	2	3
Ascites	None	Mild/Moderate	Tense
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin micromol/L (mg/dL)	<34.2 (<2)	34.2–51.3 (2-3)	>51.3 (>3)
Albumin g/L (g/dL)	>35 (>3.5)	28–35 (2.8–3.5)	<28 (<2.8)
PT (Sec over control) or INR	<4	4–6	>6
	<1.7	1.7–2.3	>2.3
CPT classification			
Child A: 5-6 points			
Child B: 7-9 points			
Child C: 10–15 points			

[2]. EV bleeding occurs at a yearly rate of 5%–15% [7]. The predictors of first bleeding include the size of varices, severity of cirrhosis (Child B or C), variceal pressure (>12 mm Hg), and the endoscopic presence of red wale marks [7, 8]. Although EV bleeding stops spontaneously in up to 40% of patients, and despite improvements in therapy over the last decade, the 6 weeks mortality rate is still  $\geq 20\%$  [9].

Gastroesophageal varices (GOV) are an extension of EV and are categorized based on Sarin's classification into 2 types (Figure 1). The most common are Type 1 (GOV1) varices, which extend along the lesser curvature. Type 2 GOV (GOV2) are those that extend along the fundus. They are longer and more tortuous than GOV1. Isolated gastric varices (IGV) occur in the absence of EV and are also classified into 2 types. Type 1 (IGV1) are located in the fundus and tend to be tortuous and complex, and type 2 (IVG2) are located in the body, antrum, or around the pylorus. When IGV1 is present, one must exclude splenic vein thrombosis. GV are less common than EV and are present in 5%–30% of patients with PH with a reported incidence of bleeding of about 25% in 2 years, with a higher bleeding incidence for fundal varices [10]. Predictors of GV bleeding include the size of fundal varices (large (>10 mm) > medium (5–10 mm) > small (<5 mm)), severity of cirrhosis (child class C>B>A), and endoscopic presence of variceal red spots (defined as localized reddish mucosal area or spots on the mucosal surface of a varix) [11].

**2.2. Ectopic Varices (EcV).** EcV are best defined as large portosystemic venous collaterals occurring anywhere in the abdomen except for the GE region [12]. They are an unusual cause of GI bleeding, but account for up to 5% of all variceal bleeding [13]. Compared to GE varices, EcV are difficult to locate, occur at distal sites, and when identified, the choice of therapy is unclear, therefore representing a clinical challenge [12]. Furthermore, bleeding EcV may be associated with poor prognosis, with one study quoting mortality reaching 40% [14]. Different areas of EcV are the duodenum,

TABLE 3: Location and blood vessels of collaterals between the portal and systemic venous circulations.

Location	Portal circulation	Systemic circulation
Gastroesophageal junction	Short gastric and left gastric (coronary) veins	Azygos vein
Rectum	Superior hemorrhoidal veins	Middle and inferior hemorrhoidal veins
Umbilical (caput medusa)	Left portal via a recannulated umbilical vein	Epigastric venous plexus of the abdominal wall
Retroperitoneum	Mesenteric veins	Intercostal, phrenic, lumbar, and renal veins

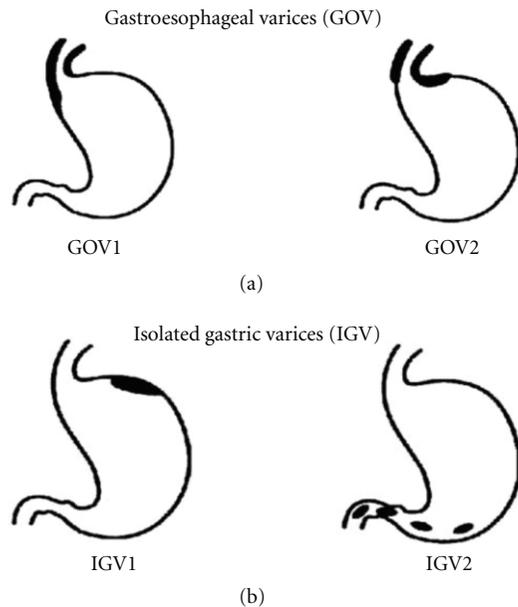


FIGURE 1: Sarin classification of gastric varices.

jejunum, ileum, colon, rectum, peristomal, biliary tree, gallbladder, peritoneum, umbilicus, bare area of the liver, ovary, vagina, and testis [15, 16].

The prevalence of EcV varies in the literature and seems to be related to the etiology of the PH and the diagnostic modalities used [17]. In patients with PH due to cirrhosis, duodenal varices are seen in 40% of patients undergoing angiography [18]. Results of a survey for EcV conducted over 5 years in Japan identified 57 cases of duodenal varices; they were located in the duodenal bulb in 3.5%, the descending part in 82.5%, and the transverse part in 14.0% [15].

In contrast to duodenal varices, it appears that most cases of varices in other portions of the small bowel and colonic varices are seen in patients with cirrhosis who have previously undergone abdominal surgery [12]. Using advanced endoscopic technologies, particularly capsule endoscopy and enteroscopy, the prevalence of small bowel varices is estimated to be approximately 69% in patients with PH [19]. The prevalence of colonic varices and rectal varices has been found to be 34% to 46% [20, 21] and 10% to 40% [22], respectively, in patients with cirrhosis undergoing colonoscopy. It is important to differentiate rectal varices from hemorrhoids; rectal varices extend more than 4 cm above the anal verge, are dark blue in color, collapse with digital pressure, and do not prolapse into the proctoscope on examination, whereas hemorrhoids do not extend proximal to the

dentate line, are purple in color, do not collapse with digital pressure, and often prolapse into the proctoscope [22, 23]. Stomal varices are a particularly common cause of EcV and can occur in patients with cirrhosis secondary to primary sclerosing cholangitis (PSC) [12].

In the west, because the prevalence of noncirrhotic PH is low, most bleeding EcV is usually associated with cirrhotic PH (6,8). Although EcV can occur at several sites, bleeding EcV are most commonly found in the duodenum and at sites of previous bowel surgery including stomas.

In a review of 169 cases of bleeding EcV, 17% occurred in the duodenum, 17% in the jejunum or ileum, 14% in the colon, 8% in the rectum, and 9% in the peritoneum. In the review, 26% bled from stomal varices and a few from infrequent sites such as the ovary and vagina [24].

Portal biliopathy, which includes abnormalities (stricture and dilatation) of both extra and intrahepatic bile ducts and varices of the gallbladder, is associated with PH, particularly extrahepatic portal vein obstruction [25, 26]. They are also seen associated with cirrhosis, non-cirrhotic portal fibrosis, and congenital hepatic fibrosis [27]. While a majority of these patients are asymptomatic, some present with a raised alkaline phosphatase level, abdominal pain, fever, and cholangitis. Choledocholithiasis may develop as a complication and manifest as obstructive jaundice with or without cholangitis [26]. On cholangiography, bile-duct varices may be visualized as multiple, smooth, mural-filling defects with narrowing and irregularity resulting from compression of the portal vein and collateral vessels. They may mimic PSC or cholangiocarcinoma (pseudocholangiocarcinoma sign) [28].

**2.3. Portal Hypertensive Intestinal Vasculopathies.** Mucosal changes in the stomach in patients with PH include portal hypertensive gastropathy (PHG) and gastric vascular ectasia. PHG describes the endoscopic appearance of gastric mucosa with a characteristic mosaic, or snake-skin-like appearance with or without red spots. It is a common finding in patients with PH [29]. The prevalence of PHG parallels the severity of PH and it is considered mild when only a mosaic-like pattern is present and severe when superimposed discrete red spots are also seen. Bleeding (acute or chronic) from these lesions is relatively uncommon, and rarely severe [30]. Patients with chronic bleeding usually present with chronic iron deficiency anemia.

In gastric vascular ectasia, collection of ectatic vessels can be seen on endoscopy as red spots without a mosaic-like pattern [31]. When the aggregates are confined to the antrum of the stomach, the term gastric antral vascular ectasia (GAVE) is used, and if aggregates in the antrum are

linear, the term watermelon stomach is used to describe the lesion. The prevalence of GAVE syndrome in cirrhosis is low [32] and can be endoscopically difficult to differentiate from severe PHG. Therefore, gastric biopsy may be required to differentiate them as histologically GAVE lesions are completely distinct from PHG (Table 4) [33].

Small bowel might also show mucosal changes related to PH, which is called portal hypertensive enteropathy (PHE). The diagnosis of PHE has been limited in the past due to the difficult access to the small bowel. With advanced endoscopic techniques such as capsule endoscopy and enteroscopy, PHE is now thought to be a frequent finding in patients with cirrhosis, perhaps as common as PHG, and may cause occult GI blood loss [34, 35].

Portal hypertensive colopathy (PHC) refers to mucosal edema, erythema, granularity, friability, and vascular lesions of the colon in PH. PHC may be confused with colitis [36, 37]. Although they are found in up to 70% of patients with PH and are more common in patients with EV and PHG, they rarely cause bleeding [38, 39].

**2.4. Ascites and Spontaneous Bacterial Peritonitis (SBP).** Ascites is defined as the accumulation of free fluid in the peritoneal cavity. Cirrhotic PH is the most common cause of ascites, which accounts for approximately 75% patients with ascites. About 60% of patients with cirrhosis develop ascites during 10 years of observation [40]. The development of ascites is an important event in cirrhosis as the mortality is approximately 50% at 2 years without a liver transplantation [41]. The formation of ascites in cirrhosis is due to a combination of abnormalities in both renal function and portal and splanchnic circulation. The main pathogenic factor is sodium retention [42].

The main clinical symptom of patients with ascites is an increase in abdominal girth, often accompanied by lower-limb edema. In some cases, the accumulation of fluid is so severe that respiratory function and physical activity is impaired. In most cases, ascites develop insidiously over the course of several weeks. Patients must have approximately 1500 mL of fluid for ascites to be detected reliably by physical examination. Dyspnea in these patients can occur as a consequence of increasing abdominal distension and/or accompanying pleural effusions. Increased intra-abdominal pressure might favour the development of abdominal hernias (mainly umbilical) in patients with cirrhosis and longstanding ascites [43].

The current classification of ascites, as defined by the International Ascites Club, divides patients in three groups (Table 5) [44]. Patients with refractory ascites are those that do not respond to sodium restriction and high doses of diuretics or develop diuretic-induced side effects that preclude their use.

Ascites may not be clinically detectable when present in small volumes. In larger volumes, the classic findings of ascites are a distended abdomen with a fluid thrill or shifting dullness. Ascites must be differentiated from abdominal distension due to other causes such as obesity, pregnancy, gaseous distension of bowel, bladder distension, cysts, and

TABLE 4: Comparison of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

FEATURE	PHG	GAVE
Relation with PH	Causal	Coincidental
Distribution in stomach	Mainly proximal	Mainly distal
Mosaic pattern	Present	Absent
Red color signs	Present	Present
Pathology		
Thrombi	–	+++
Spindle cell proliferation	+	++
Fibrohyalinosis	–	+++
Treatment	$\beta$ -adrenergic blockers TIPS/shunt surgery	Endoscopic Antrectomy and Billroth I Liver transplantation

PH: portal hypertension, TIPS: transjugular intrahepatic portosystemic shunt.

TABLE 5: International ascites club grading system for ascites.

Grade of ascites	Definition
Grade 1 ascites	Mild ascites only detectable by ultrasound
Grade 2 ascites	Moderate ascites evident by moderate symmetrical distension of abdomen
Grade 3 ascites	Large or gross ascites with marked abdominal distension

tumours. Ultrasonography is used to confirm the presence of minimal ascites and guide diagnostic paracentesis.

Successful treatment depends on an accurate diagnosis of the cause of ascites. Paracentesis with analysis of ascitic fluid is the most rapid and cost-effective method of diagnosis. It should be done in patients with ascites of recent onset, cirrhotic patients with ascites admitted to hospital, or those with clinical deterioration. The most important analyses are cell count, fluid culture, and calculation of the serum: ascites albumin gradient (SAAG), which reflects differences in oncotic pressures and correlates with portal venous pressure. If SAAG is greater or equal to 1.1 g/dL (or 11 g/L), ascites is ascribed to PH with approximately 97% accuracy [45].

Patients with cirrhosis and ascites are also at risk of developing infections, particularly spontaneous bacterial peritonitis (SBP). SBP occurs in approximately 10% of hospitalized cirrhotic patients [46], with an associated mortality of 20–40% if untreated [47]. Many patients are asymptomatic, but clinical signs can include abdominal pain, fever, and diarrhea. The diagnosis of SBP is based on neutrophil count  $>250$  cells/mm<sup>3</sup> in the ascitic fluid.

### 3. Renal Manifestations

**3.1. Hepatorenal Syndrome.** Hepatorenal syndrome (HRS) is a common complication seen in patients with advanced cirrhosis and PH [48]. HRS can also be seen in other types

TABLE 6: Revised diagnostic criteria of Hepatorenal syndrome.

(i)	Chronic or acute liver disease with advanced liver failure and portal hypertension
(ii)	Plasma creatinine concentration > 1.5 mg/dL (133 micromol/L)
(iii)	The absence of other apparent cause: shock, ongoing bacterial infection, volume depletion, current or recent use of nephrotoxic drugs
(iv)	Lack of improvement in renal function after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/day) for at least two days and withdrawal of diuretics
(v)	Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) or ultrasonographic evidence of obstructive uropathy or renal parenchymal disease

of severe chronic liver disease, alcoholic hepatitis, or in acute liver failure. This syndrome generally predicts poor prognosis [48]. HRS has been defined in the literature as a reversible functional renal impairment in the absence of other causes of renal failure, tubular dysfunction, proteinuria, or morphological alterations in histological studies. Precise and accurate diagnostic criteria have been established in order to clearly define this syndrome (Table 6) [49]. The diagnosis remains one of exclusion.

The reported incidence of HRS is approximately 10% among hospitalized patients with cirrhosis and ascites. The probability of occurrence of HRS in patients with cirrhosis is around 20% after 1 year and 40% after 5 years [50]. The pathogenesis of HRS is not completely understood, but is likely the result of an extreme underfilling of the peripheral arterial circulation secondary to arterial vasodilatation in the splanchnic circulation [51]. In addition, recent data indicates that a reduction in cardiac output also plays a significant role [52].

HRS-associated renal failure is seen in late stages of cirrhosis and is marked by severe oliguria, increased sodium and water retention, volume overload, hyperkalemia, and spontaneous dilutional hyponatremia. There are two main subtypes of HRS described [49]. Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of serum creatinine >2.5 mg/dL (>221  $\mu\text{mol/L}$ ) or a decrease of 50% in creatinine clearance (<20 mL/min) in less than 2 weeks. This form of HRS is usually precipitated by gastrointestinal bleeds, large volume paracentesis, acute alcoholic hepatitis and SBP [53]. In addition to renal failure, patients with type 1 HRS present deterioration in the function of other organs, including the heart, brain, liver, and adrenal glands. The median survival of these patients without treatment is <2 weeks, and almost all of them die within 10 weeks after onset of HRS. Type 2 HRS is a moderate and stable renal failure with a serum creatinine of >1.5 mg/dL (>133  $\mu\text{mol/L}$ ) that remains stable over a longer period and is characterized by diuretics resistant ascites [49, 54].

## 4. Neurological Manifestations

**4.1. Hepatic Encephalopathy.** Hepatic encephalopathy (HE) is defined as neurologic and psychiatric dysfunction in a patient with chronic liver disease. The exact mechanism leading to this dysfunction is still poorly understood, but multiple factors appear to play a role in its genesis. The liver normally metabolizes ammonia, produced by enteric bacteria [56] and enterocytes [57, 58]. In a patient with PH, ammonia bypasses the liver through portosystemic shunt and reaches the astrocytes in the brain. Within the astrocyte, ammonia is metabolized into glutamine, which acts as an osmole to attract water, thus causing cerebral edema. In addition, direct ammonia toxicity triggers nitrosative and oxidative stress, which lead to astrocyte mitochondrial dysfunction [59, 60]. Another important factor is the enhancement of gamma-aminobutyric acid (GABA-A) receptors through neuroinhibitory steroids (i.e., allopregnanolone) [61] and benzodiazepine. Benzodiazepine also contributes to astrocyte swelling through a specific receptor [62]. Finally, tryptophane byproducts indole and oxindole [63], manganese [64], inflammation, hyponatremia [65], and reduced acetylcholine through acetylcholinesterase activity [66] also contribute to cerebral dysfunction.

The clinical manifestations of HE can be subtle. Minimal hepatic encephalopathy (grade 0) (Table 7) can present with impaired driving ability [67], minimally impaired psychometric tests, decreased global functioning, and increased risk of falls [68]. In overt hepatic encephalopathy, diurnal sleep pattern changes will often precede neurologic symptoms. To add to the complexity, HE can be intermittent or persistent.

The severity of presentation is usually classified using the West Haven criteria (Table 7). Grade 1 hepatic encephalopathy represents lack of awareness, anxiety or euphoria, and short attention span. Change of personality, lethargy, and inappropriate behavior can be seen in grade 2 encephalopathy. More advanced features include disorientation, stupor, confusion (grade 3), and can even reach coma (grade 4). Focal neurologic symptoms, including hemiplegia, may also be observed [69]. Physical examination may be normal, but typical signs include bradykinesia, asterixis, hyperactive deep tendon reflexes and even decerebrate posturing [55].

## 5. Pulmonary Manifestations

**5.1. Hepatopulmonary Syndrome.** Hepatopulmonary syndrome (HPS) is a triad of liver disease, pulmonary vascular ectasia and impaired oxygenation. HPS is defined in the literature as a widened alveolar-arterial oxygen difference (A-a gradient) in room air (>15 mm Hg or >20 mm Hg in patients > 64 years of age) with or without hypoxemia due to intrapulmonary vasodilatation in the presence of hepatic dysfunction [70, 71]. This syndrome occurs mostly in those with PH (with or without cirrhosis) and indicates poor prognosis and higher mortality. Estimates of the prevalence of HPS among patients with chronic liver disease range from 4 to 47%, depending upon the diagnostic criteria and methods used [71–73].

TABLE 7: West Haven Criteria of Severity of Hepatic Encephalopathy (Adapted with permission [55]).

Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Lethargy or apathy Minimal disorientation for time and place Subtle personality change Inappropriate behavior Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

HPS results in hypoxemia through pulmonary microvascular vasodilatation and intrapulmonary arteriovenous shunting resulting in ventilation-perfusion mismatch [74], and can occur even with mild liver disease [75]. Clinically, patients with HPS complain of progressive dyspnea on exertion, at rest, or both. Severe hypoxemia ( $\text{PaO}_2 < 60$  mm Hg) is often seen and strongly suggests HPS [70, 71]. A classical finding in HPS is orthodeoxia defined as a decreased arterial oxygen tension by more than 4 mm Hg or arterial oxyhemoglobin desaturation by more than 5% with changing position from supine to standing. It is associated with platypnea defined as dyspnea worsened by upright position [70, 71]. Platypnea-orthodeoxia is caused by the worsening of diffusion-perfusion matching and increased shunting at the lung bases in the upright position. There are no hallmark signs on physical exam; however, cyanosis, clubbing, and cutaneous telangiectasia (spider nevi) are commonly noted. Furthermore, systemic arterioembolisation may cause stroke, cerebral hemorrhage, or brain abscess, and can present with neurological deficits.

**5.2. Portopulmonary Hypertension.** Portopulmonary hypertension (PPH), a well-recognized complication of chronic liver disease, refers to pulmonary arterial hypertension (PAH) associated with PH when no alternative causes exist. It is defined by the presence of elevated pulmonary arterial pressure (mean pressure  $>25$  mm Hg at rest and 30 mm Hg on exertion) elevated pulmonary vascular resistance ( $>240$  dyne  $\text{s}^{-1} \text{cm}^{-5}$ ) in the presence of a pulmonary capillary wedge pressure  $<15$  mm Hg [76].

The prevalence of PPH depends on the patient population studies and severity of the liver disease, 0.7–2% and 3.5–16.1% in cirrhotics and patients undergoing liver transplantation, respectively. The development of PPH is independent of the cause of PH, and it is often seen in cirrhosis. It is however, also described in those with PH due to nonhepatic pathologies such as portal venous thrombosis [71, 77]. PH seems to be the driving force of PAH. The pathogenesis of PPH is not completely understood; however, several theories have been offered. The most widely accepted theory is that

a humoral vasoactive substances (e.g., serotonin, endothelin-1, interleukin-1, thromboxane B2, and secretin), normally metabolized by the liver, is able to reach the pulmonary circulation via portosystemic shunts, resulting in PPH [71, 78, 79].

Clinically, most patients with PPH present with evidence of both PAH and PH. Typically manifestations of PH precede those of PAH. The most common presenting symptom is progressive dyspnea on exertion [80] and less frequently fatigue, palpitations, syncope, hemoptysis, orthopnea, and chest pain. On physical exam, classical features include edema, an accentuated P2 and a systolic murmur, indicating tricuspid regurgitation [71, 77, 80]. In severe cases, signs and symptoms of right-heart failure can be noted.

**5.3. Hepatic Hydrothorax.** Hepatic hydrothorax is an uncommon complication of end-stage liver disease. It is defined as a pleural effusion greater than 500 mL in patients with cirrhosis in absence of primary cardiac, pulmonary, or pleural disease [81]. The underlying pathogenesis of hepatic hydrothorax is incompletely understood. Patients with cirrhosis and PH have abnormal extracellular fluid volume regulation resulting in passage of ascites from the peritoneal space to the pleural cavity via diaphragmatic defects generally in the tendinous portion of the diaphragm [82]. Negative intrathoracic pressure during inspiration pulls the fluid from the intra-abdominal cavity into the pleural cavity. Hydrothorax develops when the pleural absorptive capacity is surpassed, leading to accumulation of fluid in the pleural space. Multiple studies have shown the passage of fluid from the intra-abdominal space to the pleural space via  $^{99\text{m}}\text{Tc}$ -human albumin or  $^{99\text{m}}\text{Tc}$ -sulphur colloid [81].

Clinical manifestations of hepatic hydrothorax include shortness of breath, cough, hypoxemia, and chest discomfort [81]. Ascites may not always be present. Hepatic hydrothorax should always be suspected in patients with cirrhosis or PH and undiagnosed pleural effusion, regardless of the presence of ascites. Serious complications include acute tension hydrothorax with dyspnoea and hypotension [83] and spontaneous bacterial empyema [84].

## 6. Other Organs Manifestations

**6.1. Cirrhotic Cardiomyopathy.** Cirrhotic cardiomyopathy is defined as a chronic cardiac dysfunction in patients with cirrhosis. It occurs in up to 50% of patients with advanced cirrhosis. It is characterized by impaired contractile response and/or altered diastolic relaxation in the absence of other cardiac diseases. The pathophysiology of this condition is complex, and seemingly related to PH and cirrhosis. In advanced liver disease, splanchnic vasodilatation leads to a resting hyperdynamic state [85]. Plasma volume expands, leading to a relative central volume decrease [86]. In cirrhosis, the arterial vessel wall thickness and tone decreases, leading to reduced arterial compliance [87, 88]. Autonomic dysfunction may also contribute to blunted cardiac response [89]. Ultimately, these factors lead to systolic and diastolic dysfunction.

Symptoms associated with cirrhotic cardiomyopathy include dyspnea with exertion, impaired exercise capacity, paroxysmal nocturnal dyspnea, peripheral edema, and orthopnea. Less-frequent presentations include long QT on electrocardiography, arrhythmia, and sudden death [90].

**6.2. Hepatic Osteodystrophy.** Hepatic osteodystrophy is defined as bone disease (osteomalacia, osteoporosis, and osteopenia) associated with liver disease. Osteomalacia and osteoporosis are frequently seen in cirrhotic patients and can predispose to pathologic fractures. The pathophysiology of osteoporosis in liver disease is relatively complex. The leading hypothesis suggests that it is related to the uncoupling of osteoblastic and osteoclastic activity. Osteoclastogenic proinflammatory cytokines (interleukin 1(IL-1) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ )) are increased in hepatic fibrosis. Moreover, TNF $\alpha$  is increased in a rat model of PH [91]. Decreased osteoblastic activity has also been linked with insulin-like growth factor 1 in a rat model (IGF-1). Increasing IGF-1 levels are associated with liver disease severity [92]. Finally, vitamin K mediates the carboxylation of glutamyl residues on osteocalcin, stimulating osteoclastic activity [93].

Patients with osteoporosis are usually asymptomatic. They may present with pain following a nontraumatic fracture of the axial skeleton or bone deformity, including pronounced cervical kyphosis. Osteomalacia presentation is similar and includes proximal muscle weakness [94].

**6.3. Hypersplenism.** Hypersplenism is a common complication of massive congestive splenomegaly in patients with cirrhosis and PH. In this condition, splenomegaly is associated with thrombocytopenia, leucopenia, or anemia or a combination of any the three [95, 96]. Severe hypersplenism is present in about 1/3 of patients with cirrhosis being assessed for liver transplantation. Most patients have no symptoms related to hypersplenism, however severe thrombocytopenia may increase the risk of bleeding, especially after invasive procedures.

## 7. Conclusion

Portal hypertension secondary to cirrhosis has multisystem effects and complications. Once a patient develops such complications, they are considered to have decompensated disease with the high morbidity and mortality. The quality of life and survival of patients with cirrhosis can be improved by the prevention and treatment of these complications.

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## Review Article

# Role of Self-Expandable Metal Stents in Acute Variceal Bleeding

**Fuad Maufa and Firas H. Al-Kawas**

*Division of Gastroenterology, Department of Medicine, MedStar Georgetown University Hospital, Georgetown University, 3800 Reservoir Road, NW, Washington, DC 20007, USA*

Correspondence should be addressed to Firas H. Al-Kawas, [alkawasf@gunet.georgetown.edu](mailto:alkawasf@gunet.georgetown.edu)

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Acute variceal bleeding continues to be associated with significant mortality. Current standard of care combines hemodynamic stabilization, antibiotic prophylaxis, pharmacological agents, and endoscopic treatment. Rescue therapies using balloon tamponade or transjugular intrahepatic portosystemic shunt are implemented when first-line therapy fails. Rescue therapies have many limitations and are contraindicated in some cases. Placement of fully covered self-expandable metallic stent is a promising therapeutic technique that can be used to control bleeding in cases of refractory esophageal bleeding as an alternative to balloon tamponade. These stents can be left in place for as long as two weeks, allowing for improvement in liver function and institution of a more definitive treatment.

## 1. Introduction

Acute variceal bleeding continues to be associated with significant mortality. Recently published randomized controlled trials have shown that mortality from acute variceal bleeding has decreased over the past two decades from 42% to 15%, but this figure is still remarkably high [1]. Current recommendations for the treatment of acute variceal bleeding are to combine hemodynamic stabilization, antibiotic prophylaxis, pharmacological agents, and endoscopic treatment [2]. Endoscopic therapy using band ligation combined with vasoactive drugs is highly effective. First line therapy however may fail to control bleeding or is associated with early rebleeding (within five days) in as many as 10–20% of patients [2]. These patients are treated with rescue therapies including balloon tamponade (BT), insertion of a transjugular intrahepatic portosystemic shunt (TIPS), or surgical shunts.

## 2. Limitations of Current Rescue Therapies

**2.1. Balloon Tamponade.** Balloon tamponade (BT) using Sengstaken-Blakemore tube used to be the primary therapy

prior to the availability of endoscopic methods. Sengstaken-Blakemore tube, was first described in 1950 [3], is a multi-luminal plastic tube with two inflatable balloons (esophageal and 250 cc gastric balloons). Minnesota tube is a modified Sengstaken-Blakemore tube with an esophageal suction port. Linton-Nachlas tube has a single 600 cc gastric balloon. BT is effective in controlling bleeding at least temporarily, in over 80% of patients [2, 4–7]. Bleeding recurs after deflation in over 50% of cases [2, 4]. The most common error limiting the efficacy of tamponade is failure to position the gastric balloon correctly at the gastroesophageal junction [8]. It is seldom necessary to inflate the esophageal balloon if the gastric balloon is correctly positioned. BT should be only used as temporary bridge to control massive bleeding until more definitive therapy could be instituted within 24 hours [7, 9]. Use of BT requires appropriate expertise. Rate of complications is increased and efficacy is limited if the tube is placed by inexperienced operator. BT is associated with fatal complications in 6–20% of cases [4]. The most serious complication is the esophageal rupture following inflation of gastric balloon in the esophagus [10, 11]. Proximal tube migration can lead to asphyxiation [12]. Prolonged inflation of esophageal and gastric balloon can lead to esophageal

and gastric ulceration from pressure necrosis. Aspiration is frequent after tube insertion and occurs in 10–20% of patients. The presence and degree of encephalopathy may be a contributing factor. Aspiration may be prevented by elective endotracheal intubation prior to insertion of BT [6, 7]. The presence of the tube is highly unpleasant for the patient and repeated endoscopic examinations may be difficult.

**2.2. Surgical Management.** Surgical management for bleeding esophageal varices falls into two categories: shunt and nonshunt procedures. Nonshunt procedures include esophageal transection and gastroesophageal devascularization. Shunt procedure is classified into selective shunts such as splenorenal shunts, partial shunts such as calibrated small-diameter portacaval shunts, and nonselective shunts such as portacaval shunts. Surgical procedures are used less frequently in the era of advanced endoscopic therapy, TIPS, and liver transplant. However, surgical intervention remains an important and effective treatment modality in selected patients [13]. Distal splenorenal shunts and nonselective shunts are very effective in controlling bleeding [4]. These procedures are more protective against rebleeding than gastroesophageal devascularization [13]. Modified Sugiura procedure (transabdominal gastroesophageal devascularization + esophageal stapled transection + splenectomy) can be a life-saving procedure in patients with anatomy unsuitable for shunt surgery or for patients treated in nonspecialized centers where surgical expertise for a shunt operation is not available [14]. Despite of effectiveness of surgical procedures, mortality remains high (45–75%) [4, 15] and hepatic encephalopathy continues to be an important complication even in selective shunt procedures [4]. The calibrated small-diameter portacaval shunt was reported to have lower rate of hepatic encephalopathy compared to nonselective shunt in one randomized clinical trial but this remains to be replicated by other investigators [16].

**2.3. Transjugular Intrahepatic Portosystemic Shunt (TIPS).** TIPS is an intrahepatic shunt that is placed using a percutaneous approach. It connects the hepatic vein and intrahepatic branch of portal vein using an expandable metallic stent with a diameter of 8 to 12 mm. TIPS was introduced as an alternative to surgery in the 1990s and has replaced surgical shunts in most centers [17]. Current practice guidelines reserve TIPS for patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy. TIPS is extremely effective in controlling variceal bleeding with a reported rate of immediate hemostasis of 95% and with rebleeding in only 18% of patients [18]. However, worsening of liver function and encephalopathy continue to be a problem and mortality remains high because of further deterioration due to liver failure [4]. In some studies, 30–35% of patients developed hepatic encephalopathy following TIPS [19]. The current use of TIPS as rescue therapy was challenged in a recent study where early use of TIPS in high-risk patients (Child-Pugh

class C or those in class B who have persistent bleeding) was reported to be associated with improved outcome and reduction in mortality [20]. Insertion of TIPS is technically challenging and may not be available in some centers, thus necessitating the need to transfer a critically ill patient. Occlusion of the hepatic or portal veins may preclude TIPS placement.

The previously listed limitations of the current rescue therapies have led to the continued search for other methods as rescue therapy for refractory esophageal variceal bleeding.

### 3. Self-Expandable Metal Stent in Treatment of Refractory Esophageal Variceal Bleeding

Self-expandable metal stents (SEMSs) are increasingly used in treatment of esophageal obstruction, stricture, leak, perforation, and tracheoesophageal fistula [22]. Anecdotal experience suggests that the covered version of these stents may be helpful in controlling bleeding esophageal varices. However, minimal published data is available and issues related to efficacy of insertion and safety need to be clarified. Recently, a specially designed SEMS for the treatment of refractory esophageal variceal bleeding became available [23]. The SX-Ella Danis stent (Ella-CS, Hradec Kralove, Czech Republic) is removable, covered SEMSs that can be deployed in the lower esophagus over an endoscopically placed guide wire without radiological assistance (Figure 1) [21]. The stent has atraumatic edges and radiological markers at both ends and at the midpoint to easily assess its position by a plain chest X-ray. Retrieval loops with gold markers at both stent ends allow the endoscopic extraction of the stent. In general, during endoscopy, a guide wire is placed in the stomach under direct vision and the endoscope is removed. The stent delivery device is then advanced over the guide wire into the stomach, and the distal portion of the stent delivery system is withdrawn to allow inflation of the gastric balloon. The gastric balloon is then inflated with air, and the whole delivery system is withdrawn until resistance is felt, which signifies that the balloon is impacting at the cardia. After stent deployment, the gastric balloon is deflated and the stent delivery system is withdrawn. The stent controls bleeding by tamponade of varices in the lower esophagus. The stent can be left in place for as long as two weeks. Stents can be removed using a special extractor device provided with the stent kit (PEX-Ella extractor device). Four published case series evaluated the effectiveness and safety of this stent in treatment of refractory esophageal variceal bleeding [21, 23–25]. “Refractory esophageal variceal bleeding” refers to ongoing bleeding despite pharmacological and endoscopy therapy. A summary of findings is listed in Table 1.

The initial pilot study by Hubmann et al. in 2006 reported the use of SEMS in 20 patients with massive ongoing esophageal variceal bleeding [23]. All patients failed prior endoscopic or pharmacological therapy. In this study, SEMSs were used as an alternative to balloon tamponade. Eight patients were Child-Pugh grade B and 12 grade C. Standard esophageal SEMS were used in the initial five patients. Choo stents (diameter 18 mm, length 140 mm;

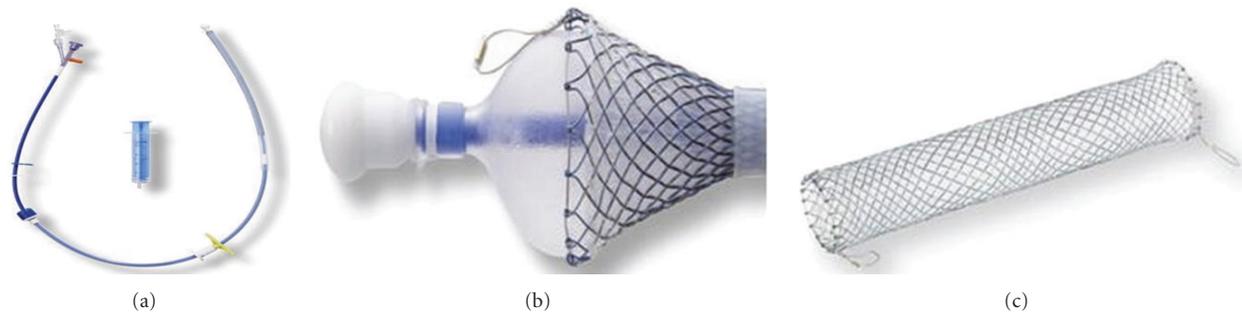


FIGURE 1: (a) The SX-Ella DANIS stent is supplied preloaded in an insertion device that has a 26 F diameter and is 60 cm long. (b) A balloon at the distal end of the insertion device (shown partially inflated) allows anchoring of the distal end of the stent at the cardia during deployment. (c) The fully deployed stent is 135 mm long and 25 mm wide [Reprinted from [21]].

TABLE 1: Published series using SEMS for refractory esophageal variceal bleeding.

	Year of publication	Number of patients	% of success of placement of SEMS	% of control of bleeding	Stent migration	Recurrent bleeding	Local complications	Mortality
Hubmann et al. [23]	2006	20	100%	100%	25%	0	One minor esophageal ulcer.	Two died within 5 days.
Zehetner et al. [24]	2008	39	100%	100%	18%	0	One minor esophageal ulcer.	30-day mortality 26.5%.
Wright et al. [21]	2010	10	90%	70%	Not reported.	1 rebleeding at 60 days.	Small proximal esophageal ulcer.	42-day mortality 50%.
Dechéne et al. [25]	2012	8	100%	88%	0%	3 rebleeding.	Compression of left main bronchus.	60-day mortality 75%.

NES-18-080-070, M.I. Tech Co., Ltd) were used in two and the Ella-Boubela-Danis stent (diameter 20 mm, length 95 mm; Ella-CS, Hradec Kralove, Czech Republic) was used in three patients. In the remaining 15 patients, the newly designed Ella-Danis stent (diameter 25 mm, length 135 mm) was used. The stents were inserted using special introducer that allows placement of the stent without radiological or even endoscopic control. Correct insertion was accomplished by inflating the balloon at the distal end of the insertion device. The balloon was retracted to the cardia before release of the stent allowing correct positioning. After release of the stent, the balloon was deflated and the insertion device was removed. Upper endoscopy was performed after stent placement. A chest X-ray was obtained 12 hours after placement to confirm correct stent position. Stent placement was successful and bleeding was controlled immediately in all but one patient. This patient continued to bleed from gastric varices and underwent surgery (total gastrectomy and an open azygoportal disconnection) to control the bleeding. The remaining 19 patients were stable within two hours. No rebleeding occurred during 30-day followup. Stent migration to the stomach was reported in five patients with no apparent complications or rebleeding. Only 2/15 patients with the SX-Ella Danis stent had migration. Apparently, migrating stents were repositioned with endoscopy. All stents were extracted using standard endoscopy and a special

foreign-body extractor (2–14 days after placement) with no complications. One patient was found to have a small ulceration in the distal esophagus. Two patients died 3 and 5 days after stent placement due to multiple organ failure. One of these patients had esophageal rupture caused by a Sengstaken tube used before the stent procedure. Neither of these patients had recurrent bleeding from the varices. After stent extraction, the remaining 18 patients underwent evaluation for definitive treatments. The main procedures in these patients were TIPS (5 patients), laparoscopic azygoportal disconnection (5 patients), band ligation (4 patients), and interventional radiography-guided coiling (1 patient). Liver transplant was eventually performed in three of these patients.

Hubmann et al. published their extended series of 39 patients with massive ongoing esophageal variceal bleeding despite prior use of endoscopic or pharmacological therapy [24]. Results were similar to the previous report (20 of 39 patients were the same group of patients used in the previous report). In this study SEMS was again used as an alternative to balloon tamponade. SX-ELLA Danis stent was used. The technique of the implantation was similar to the previous published series. Stent placement was successful and uncomplicated for all patients. Bleeding was stopped in all patients. Stents were extracted with a special designed extractor. One patient was found to have a minor esophageal

ulcer but no other local complications reported. Stent migration to the stomach was observed in seven patients. The 30-day mortality rate was 26.5%. None of the patients experienced bleeding recurrence. Definitive therapy was employed in most of the patients after stent extraction. The principal procedure was band ligation in 11 patients, TIPS insertion in 8 patients, and laparoscopic azygoportal disconnection in 5 patients. Two patients were put on a liver transplant list.

Wright et al. reported their experience using the SX-Ella Danis stent in ten patients with variceal bleeding and contraindications to TIPS insertion or balloon tamponade [21]. The patients were not considered candidate for TIPS because of the multiple organ failure, severe liver disease, or the presence of hepatocellular carcinoma. Two patients had BT-induced esophageal tears. The stent was delivered using a technique similar to the previous studies. In one patient, the stent was placed without prior endoscopy because of severity of bleeding. Stents were placed successfully in 9 of the 10 patients. The failed deployment was caused by failure of the gastric balloon to inflate. Nine patients were actively bleeding at the time of stent insertion; in these patients, immediate control of bleeding was observed in 7 patients after stent insertion. In the remaining two patients, the source of bleeding was subsequently confirmed to be from gastric varices. Six of 9 successfully stented patients survived the acute bleeding episode. No information was given about stent migration. In one patient, the stent was removed under fluoroscopic control. In the remaining patients, stents were extracted successfully with the PEX-Ella extractor device at a median of 9 days (range 6–14 days). No major local complications were reported. One patient had esophageal ulcer related to the proximal end of the stent. Using Baveno IV consensus criteria, failure to control bleeding was observed in 3 patients (one patient died of multiple organ failure two days after stent insertion and two patients died of exsanguination). The 42-day survival rate was 50%. There was one episode of rebleeding 60 days after stent removal.

Dechêne et al. recently reported their experience using SEMS (SX-Ella Danis; stent Ella-CS, Hradec Kralove, Czech Republic) in 8 patients with refractory esophageal variceal bleeding events [25]. One patient was treated twice over a period of 7 months. Source of bleeding was confirmed to be esophageal varices in all cases and excluded patients bleeding from gastric varices. Balloon tamponade was used in 3 patients prior to transportation to the tertiary center. SEMSs were placed successfully in all patients. The proper stent position and cessation of bleeding was confirmed by upper endoscopy. Control of bleeding was successful in 8/9 bleeding episodes (one patient died within five days of presentation). All stents were removed successfully after a median of 11 (7–14) days with no immediate rebleeding. No stent migration occurred in this series. The only complication related to the stent was compression of the left main bronchus which was treated successfully with stent removal. Definitive therapy was feasible in two patients (OLT and TIPS) and no rebleeding was noted in this group. TIPSs were contraindicated in the remaining six patients due to hepatic

failure, hepatic encephalopathy, or hepatocellular carcinoma. Three patients had rebleeding 1, 2, and 9 days after stent removal. The 60-day survival rate was 25%.

Standard fully covered SEMSs have also been used successfully for the management of esophageal tears caused by Sengstaken-Blakemore tube or banding. These applications further confirm the important role of SEMS in the successful management of iatrogenic esophageal injuries [21, 26, 27].

#### 4. Indications and Benefits

Limited data suggests that specially designed SEMS (SX-Ella Danis stent) can effectively stop refractory bleeding from esophageal varices (Table 1). This stent is usually deployed over an endoscopically placed wire without the need for radiological control. Limited data suggest that stent can also be delivered even without endoscopic assistance and without the need for continued endotracheal intubation compared to BT. Oral intake and nutrition are maintained. Stents can be left in place for as long as two weeks, allowing for improvement in liver function and institution of secondary prophylaxis before removal. Overall, compared to BT, SEMSs appear to be as effective, easier to insert and are associated with a lower risk for complications. Repeat endoscopy, if needed, can be performed while stent is in place.

#### 5. Limitations and Complications

Stent placement requires appropriate training and expertise. Gastric varices will not be adequately compressed by the stent and persistent variceal bleeding after stent placement should raise the suspicion for presence of bleeding gastric varices. Appropriate precautions to prevent aspiration are needed since the stent is positioned at the gastroesophageal junction. Distal stent migration into the stomach was observed frequently but was not associated with apparent complications. Stent-related compression of the left main bronchus was reported in one patient and was treated successfully with stent removal [25, 28]. No reports of esophageal wall hyperplasia as seen with other esophageal indications have been published. However, all stents need to be removed within 1-2 weeks to minimize the risk of migration and wall injury or reaction. Table 2 summarizes indications, efficacy, benefits, and limitations of the current rescue therapies in refractory esophageal variceal bleeding.

#### 6. Conclusion

Current rescue therapies for bleeding esophageal varices are effective in stopping the bleeding in the majority of patients (Table 2). In some patients, standard therapies may fail, are associated with serious complications, or may not be possible to use because of patient characteristics. SEMS placement using especially designed stent (SX-Ella Danis stent, currently not available in USA) is a new promising alternative therapeutic technique that can be used in patients with refractory esophageal variceal bleeding. Patients who failed initial standard therapy, have contraindications, or

TABLE 2: Rescue therapies for refractory esophageal variceal bleeding.

Modality	Candidate	Efficacy in controlling bleeding	Complications	Limitation
BT	Refractory esophageal bleeding as bridge to definitive therapy.	More than 80% but tube should be removed within 24 hours.	Potentially lethal complications including esophageal perforation aspiration and pneumonia.	Limited efficacy and high complication rate in in-experienced hands. Temporary measure.
Surgery	Acute variceal bleeding unresponsive to medical and endoscopic therapy.	Heterogeneous group but generally very effective.	Hepatic encephalopathy. Liver decompensation.	Requires expertise with exception of modified Sugiura procedure.
TIPS	Acute variceal bleeding unresponsive to medical and endoscopic therapy.	More than 90%.	Hepatic encephalopathy. Liver decompensation.	Limited availability Occlusion and stenosis. Not suitable or contraindicated in many patients.
SEMSs	Refractory esophageal bleeding as bridge to definitive therapy.	70–100% and stent can be left in place for as long as 2 weeks.	Minor esophageal ulcer. Migration. Compression of left main bronchus.	Temporary measures Require a repeat endoscopy for removal.

are unsuitable for those therapies are good candidates at this time. Limited data suggests that when stent and expertise are available, these SEMSs can be considered as an alternative to BT. Use of SEMS is considered only as a bridge allowing stabilization of the patients until more definitive therapy is performed (banding, TIPS, shunt surgery, or liver transplant). The applicability of data using the specialized SEMS (SX-Ella Danis stent) to other currently available fully covered esophageal stents is not clear at this time. However, all fully covered SEMS can be used to manage iatrogenic esophageal injuries associated with the use of BT or banding. Further studies are needed to confirm safety and efficacy of SEMS in a large group of patients with bleeding esophageal varices and to establish their role in the management of such patients.

## Abbreviations

BT: Balloon tamponade

TIPS: Transjugular intrahepatic portosystemic shunt

SEMS: Self-expandable metal stent.

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## Review Article

# The Transjugular Intrahepatic Portosystemic Shunt in the Treatment of Portal Hypertension: Current Status

**Gilles Pomier-Layrargues,<sup>1</sup> Louis Bouchard,<sup>2</sup> Michel Lafortune,<sup>2</sup> Julien Bissonnette,<sup>1</sup> Dave Guérette,<sup>1</sup> and Pierre Perreault<sup>2</sup>**

<sup>1</sup> *Liver Unit, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada H2X 3J4*

<sup>2</sup> *Department of Radiology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada*

Correspondence should be addressed to Gilles Pomier-Layrargues, gilles.pomier.layrargues@umontreal.ca

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The transjugular intrahepatic portosystemic shunt (TIPS) represents a major advance in the treatment of complications of portal hypertension. Technical improvements and increased experience over the past 24 years led to improved clinical results and a better definition of the indications for TIPS. Randomized clinical trials indicate that the TIPS procedure is not a first-line therapy for variceal bleeding, but can be used when medical treatment fails, both in the acute situation or to prevent variceal rebleeding. The role of TIPS to treat refractory ascites is probably more justified to improve the quality of life rather than to improve survival, except for patients with preserved liver function. It can be helpful for hepatic hydrothorax and can reverse hepatorenal syndrome in selected cases. It is a good treatment for Budd Chiari syndrome uncontrollable by medical treatment. Careful selection of patients is mandatory before TIPS, and clinical followup is essential to detect and treat complications that may result from TIPS stenosis (which can be prevented by using covered stents) and chronic encephalopathy (which may in severe cases justify reduction or occlusion of the shunt). A multidisciplinary approach, including the resources for liver transplantation, is always required to treat these patients.

## 1. Introduction

Portal hypertension is associated with severe and often life-threatening complications. Increased intrahepatic resistance results in increasing splanchnic blood flow and development of venous collaterals, which may bleed, and also causes splenomegaly. A hyperdynamic circulation develops with an increased cardiac output and a decrease in systemic vascular resistance. Pooling of splanchnic blood may result in a systemic hypovolemia, which can trigger activation of vasoactive systems, mainly vasoconstrictors. This in turn may lead to sodium retention, ascites, and ultimately hepatorenal syndrome [1]. The correction of severe portal hypertension by portacaval shunt surgery has been used for many years, but the morbidity and mortality were high. Moreover, this technique was contraindicated in the presence of liver failure.

The transjugular intrahepatic portosystemic shunt (TIPS) was used for the first time by Rösch et al. in 1969 [2]

in dogs and in a cirrhotic patient by Colapinto in 1982 [3]. This treatment was aimed at nonsurgically decreasing portal hypertension. Originally, a tract was created by balloon dilatation of the parenchyma between the hepatic vein and the portal vein after transjugular portal vein catheterization. Unfortunately, this communication closed within days after the procedure. In 1989, the first case of TIPS created with a metallic stent was published by Rössle et al. [4]. This technical advance allowed good long-term patency of the shunt.

Many papers were published in the following years, which led to technical improvements and definition of the best indications for this promising treatment of complications of portal hypertension [5].

In the present paper, technical aspects of this procedure will be described, and the current indications based on the existing literature will be discussed. Contraindications (absolute and relative) will be reported and the potential

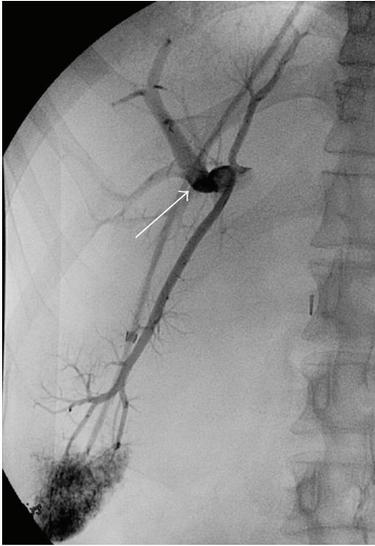


FIGURE 1: Wedged hepatic venography allowing intrahepatic portal vein localisation (arrow).

complications following the TIPS procedure as well as their treatment will be mentioned.

## 2. Technical Aspects

TIPS is a hemodynamic equivalent of a side-to-side small diameter surgical portacaval shunt. The experience gained over the last 20 years allows thorough evaluation of the complications of this technique and of its contraindications and indications [5, 6].

This technique is preferably done under general anesthesia [7] but can be performed with deep sedation (particularly for emergency cases). Antibiotic prophylaxis is given even if the literature has not proven the usefulness of this approach, and coagulation defects are corrected before the procedure. After puncture of the jugular vein (most often the right jugular vein) under echographic guidance, a catheter is introduced into one hepatic vein and wedged in the liver parenchyma. Gentle injection of dye allows the retrograde visualisation of intrahepatic portal vein branches [8] (Figure 1). The intrahepatic portal vein then is entered with a modified Ross needle (Cook Medical, Bloomington, IN, USA). CO<sub>2</sub> can be used in patients with renal function impairment to avoid dye nephrotoxicity. Several TIPS sets are commercially available. A guide wire is advanced into the main portal vein. The tract between the hepatic and the portal vein is dilated with an angioplasty balloon catheter (8–10 mm) (Figure 2) followed by stent placement to maintain the communication between both vessels patent (Figure 3). Various TIPS stents can be used (bare stents and PTFE-covered stents). The portacaval gradient after TIPS must be lower than 12 mmHg (the cut-off level associated with complications of portal hypertension) [1, 9].

This technique is now well standardized in specialized centers. The use of ultrasound or transhepatic portography can help localize the intrahepatic portal vein, particularly when anatomic variants or marked liver distortion is

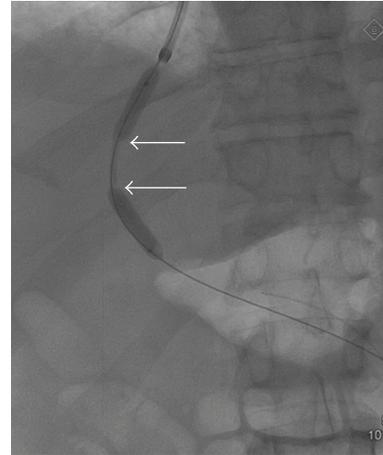


FIGURE 2: Tract dilatation using a 10 mm angioplasty balloon catheter. The narrowed part of the balloon is in the intraparenchymal part of the tract (arrows).

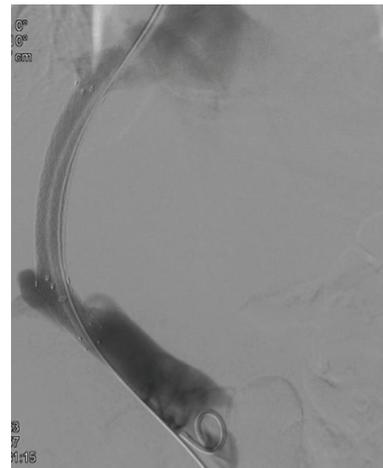


FIGURE 3: TIPS made with PTFE-covered stents between portal and right hepatic veins.

observed particularly in cirrhotic patients [8, 10]. Over the years, PTFE-covered stents have replaced bare stents as they markedly improved the long-term patency of the shunt and also prevent portobiliary fistulae [11–13]. The metallic stent should be placed near the junction between the hepatic vein and the vena cava and no more than 1–2 cm below the bifurcation of right and left portal veins. Moreover, the covered part of the stent should not be inside the portal vein as it can block the retrograde intrahepatic portal flow, which may result in intrahepatic portal vein thrombosis. Provided that these principles are followed, liver transplantation can be performed safely without interference of the stent at the time of portal vein and vena cava clamping [14, 15].

## 3. Contraindications

Contraindications are summarized in Table 1. As mentioned previously, portal hypertension is associated with a hyperdynamic circulation (increased cardiac output, increased

TABLE 1: Contraindications for the TIPS procedure.

Absolute
(i) Right sided heart failure
(ii) Biliary tract obstruction
(iii) Uncontrolled infection
(iv) Pulmonary hypertension
(v) Chronic recurrent disabling hepatic encephalopathy
(vi) Hepatocellular carcinoma involving hepatic veins
Relative
(i) Severe liver failure (Pugh score >12)
(ii) Portal vein thrombosis
(iii) Multiple hepatic cysts

splanchnic blood flow and decreased systemic resistances). Hemodynamic changes induced by TIPS are spectacular, with a sudden increase in the cardiac output secondary to diversion of splanchnic blood flow into the systemic circulation [16, 17]. Therefore, any impairment in the right ventricle function before TIPS is a problem, as congestive liver failure may be observed after TIPS-induced increase in cardiac output. An evaluation of cardiac function is required before TIPS. On the other hand, even if the hyperdynamic circulation worsens after the procedure, this phenomenon is often transient [16]. The other contraindications are quite obvious. Pre-TIPS chronic recurrent disabling hepatic encephalopathy (HE) is an absolute contraindication, but the onset of an episode of HE induced by precipitants (such as bleeding, sepsis, electrolyte imbalance) before TIPS does not preclude the use of this procedure. The presence of portal vein cavernoma or portal vein thrombosis is no longer an absolute contraindication and may even become an indication as technical advances allow recanalization of the portal vein in some selected cases [18–21]. A transhepatic or a transplenic approach can be helpful to catheterize the main portal vein and facilitates the TIPS procedure.

Many prognostic studies have been published for the prediction of short-term survival after TIPS [22–24]. It is now well recognized that a Pugh score higher than 12 most often represents a contraindication as multiorgan failure occurs in a vast majority of these cases after TIPS [6]. The Meld score has been initially validated as the best predictor of the 3 months survival rate [25–27]. However, TIPS may be performed as a temporary hemostatic measure in a patient already placed on the waiting list for liver transplant.

#### 4. Complications

They are summarized in Tables 2 and 3. Comparison of complication frequency is difficult to evaluate in the literature due to the patient characteristics, the expertise of the center and the study period [28, 29].

**4.1. Acute Complications.** Acute complications might occur during TIPS placement or within hours or days after the procedure and include neck hematoma, arrhythmia, stent displacement, hemolysis, bilhemia, and shunt thrombosis.

TABLE 2: Acute complications after TIPS placement.

Minor or moderate
(i) Neck hematoma
(ii) Arrhythmia
(iii) Stent displacement
(iv) Hemolysis
(v) Bilhemia
(vi) Hepatic vein obstruction
(vii) Shunt thrombosis
life threatening
(i) Hemoperitoneum
(ii) Hemobilia
(iii) Liver ischemia
(iv) Cardiac failure
(v) Sepsis

TABLE 3: Chronic complications after TIPS placement.

(i) Congestive heart failure
(ii) Portal vein thrombosis
(iii) Progressive liver failure
(iv) Chronic recurrent encephalopathy
(v) Stent dysfunction
(vi) “TIPSitis”

Neck hematoma can be prevented by haematological preparation and ultrasound-guided puncture of the jugular vein. Arrhythmia may occur but is self-limited when the distal tip of the guide wire is removed from the right atrium. Bilhemia results from a fistula between a biliary radicle and the portal vein. It must be suspected when a sudden rise of direct bilirubin occurs without any symptoms. It can be proven by shuntography or ERCP and treated by a covered stent across the fistula [30, 31]. Hemolysis is transient and is related to the fragmentation of red blood cells in the metallic stent before endothelialization [32, 33]. The obstruction of a small hepatic vein by a PTFE-covered stent may induce a “segmental” Budd Chiari syndrome with a transient increase in serum bilirubin and transaminases. This phenomenon is self-limited in a majority of the cases [34, 35]. Acute shunt thrombosis (less than 5%) is rare and it is usually due to a portobiliary fistula or in some cases to stent malfunction [36, 37]. The usefulness of phenprocoumon to prevent stent thrombosis is not well established [38]. The shunt can be recanalized but at the same time the fistula must be closed with a covered stent.

Life-threatening complications are very rare (less than 1%) and include hemoperitoneum, hemobilia, liver ischemia, cardiac failure, and sepsis [28]. Hemoperitoneum is most often related to a puncture of the liver capsule; it is usually self-limited. A dissection of the portal vein in its extrahepatic part is life threatening and can be treated with a covered stent. Hemobilia results from a procedure-related fistula between a hepatic artery and the biliary tract. It is treated by embolization. Liver ischemia may follow

TABLE 4: Risk factors for post-TIPS encephalopathy.

Age
Gender
Etiology
HE before TIPS
Child-Pugh score
Portohepatic gradient
Shunt diameter
Creatinine
Indication

an accidental catheterization of an intrahepatic artery followed by its thrombosis [39, 40]. Cardiac failure is due to a rapid increase in cardiac output; it may be severe and diuretics can be tried but, in life threatening cases, the obstruction of the shunt may be needed. Finally, sepsis is a potential complication, but antibioprophyllaxis can prevent it in a vast majority of cases.

**4.2. Chronic Complications.** Chronic complications are more frequent and their management may be difficult. Congestive heart failure is related to a high cardiac output following TIPS. Clinically the patients develop sodium retention and right sided heart failure; in severe cases, treatment with diuretics and vasodilators does not work and obstruction of the shunt may be necessary. Portal vein thrombosis is very rare. It occurs more often when the stent is not correctly placed inside the portal or the hepatic vein, thus obstructing the shunt flow [8]. It may be observed in patients with a hypercoagulable state and in this situation life-long anticoagulation is needed. As observed after surgical portacaval shunt, progressive liver failure may follow TIPS implantation. The first sign is a progressive increase in the serum bilirubin, which is then followed by a rise in INR, onset of encephalopathy, and death due to multiorgan failure within weeks after TIPS. Even if poor pre-TIPS liver function is a risk factor, some patients with a good hepatic reserve may also develop this serious complication after TIPS. Liver transplantation is the only option in this situation.

TIPS is a portacaval shunt; therefore, not surprisingly post-TIPS HE remains a problem. HE episodes are observed in 30–40% of cirrhotic patients, and as opposed to that observed in patients without TIPS, no precipitant can be identified in a majority of cases.

Chronic recurrent disabling HE can occur in 5–10% and may lead to a complete loss of the patient's autonomy. Several pre-TIPS parameters have been tested to predict post-TIPS hepatic encephalopathy (Table 4). Age, pre-TIPS encephalopathy, and the Pugh score are probably the most useful predictors [41–49]. Prophylaxis with lactulose is not useful [50]. The medical management is difficult and in many cases the only option is to reduce the diameter of the stent or preferably to occlude it [51]. HE clears quickly after the obstruction, but portal hypertension recurs with its associated potential complications (ascites and variceal bleeding). Embolization of varices before TIPS occlusion might be useful measure to prevent variceal rebleeding.



FIGURE 4: Portography in patient treated one year ago with a TIPS made of a combination of one PTFE-covered stent and one bare stent. Pseudointimal hyperplasia developed only on the bare part of the TIPS (arrows) and induced TIPS dysfunction.

The function of the TIPS is usually evaluated using Doppler ultrasonography. The direction of intrahepatic portal flow, the flow volume in the stent, and the presence of increased velocity in the stent are useful criteria to detect shunt dysfunction and to decide if a shunt revision is needed with an angiographic intervention [52, 53]. However, the sensitivity and specificity of this modality are only 80–85%. Shunt dysfunction results from an intimal hyperplasia in the stent [54] and is more frequent in the hepatic vein part of the shunt (Figure 4). This phenomenon was observed at 1 year in nearly 80% of cases treated with bare stents and could not be prevented with acetyl salicylic acid [55] or trapidil + ticlopidine [56]. When PTFE-coated stents are used the one-year rate of shunt stenosis is only 10–15% [12] (Figure 3). Treatment includes dilatation of the stenoses and/or implantation of a new covered stent in this area. TIPS involves a foreign material chronically implanted in the liver, and cirrhotic patients are often immunocompromised and therefore susceptible to infection. But, surprisingly, the infection of the stent (the so-called TIPSitis) is exceptional [5]. Diagnostic criteria include repeated episodes of septicaemia without any other detectable source of infection. It is best treated with long-term antibiotherapy [57, 58].

## 5. Indications

TIPS has been used to treat many complications related to portal hypertension. The relative efficacy of TIPS has been tested with randomized controlled trials, (refractory ascites, variceal bleeding), whereas other indications have been evaluated in uncontrolled case series.

### 5.1. Gastrointestinal Bleeding

#### 5.1.1. Oesophageal Variceal Bleeding

**Primary Prophylaxis.** Bleeding from oesophageal varices is a common and severe complication of portal hypertension.

TABLE 5: Comparison of TIPS and endoscopic and/or pharmacological therapy in the prevention of oesophageal variceal rebleeding (from Zheng et al. [59]).

Treatment	Number of patients	Rebleeding rate <i>n</i> (%)	Encephalopathy <i>n</i> (%)	Mortality <i>n</i> (%)
TIPS	440	86 (19)	148 (33)	111 (26)
Sclerotherapy /pharmacological therapy	443	194 (44)	86 (19)	98 (22)

Prevention of the initial bleeding can be achieved in a number of cases by endoscopic variceal ligation or  $\beta$ -blocker treatment. However, TIPS has never been tested in this situation as previous experience with surgical portacaval shunts has clearly demonstrated that this approach is associated with higher morbidity and mortality rates [60].

**5.1.2. Acute Bleeding Episode.** When an initial bleeding occurs, it is usually controlled with less invasive endoscopic treatment and/or pharmacological therapy. In rare cases bleeding remains uncontrollable, and TIPS has been used as a rescue treatment with good results for bleeding control. However, prognosis relies on the general condition of the patient, the value of the liver function reserve, and the associated comorbidities [61–64]. However, a recent randomized controlled trial evaluated the use of emergent TIPS as compared to standard medical therapy in patients with severe portal hypertension and a Pugh score of 7 to 13 [65]. Treatment failure was more frequent in the medical group (50% versus 12%) and the survival rate was better in the TIPS group (11 versus 38%). This approach could justify the use of TIPS early after bleeding episodes in patients with moderate or severe liver failure and severe portal hypertension. These promising results are in line with that observed in a case series of cirrhotic patients Child A or B who underwent emergency portacaval shunt surgery [66] but should be confirmed by other controlled trials.

**5.1.3. Secondary Prophylaxis.** Bleeding tends to recur frequently after a first episode.  $\beta$ -blockers and variceal band ligation have both been demonstrated to lower the incidence of rebleeding [1]. TIPS has been tested against these two modalities in several prospective controlled trials [67–78]. Meta-analyses have demonstrated that TIPS was more efficient in preventing rebleeding but it was more frequently followed by episodes of encephalopathy, and survival was not different between groups [59, 79, 80] (Table 5). TIPS has also been compared with surgical shunts or oesophageal transaction [81–83], but results are difficult to interpret because all the patients were good operative risks, and the studies were performed before the introduction of PTFE-coated stents. Therefore, TIPS is not recommended as a first-line therapy for secondary prophylaxis of variceal bleeding.

**5.1.4. Gastric Variceal Bleeding.** Bleeding from gastric varices is often severe and difficult to control, particularly when fundal varices are involved. The first-line treatment is endoscopic sclerotherapy with cyanoacrylate [84]. TIPS has been used in a number of uncontrolled trials in patients in whom endoscopic therapy failed [85, 86]. A recent controlled

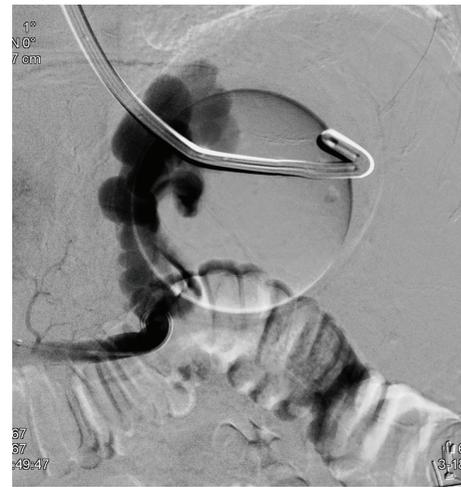


FIGURE 5: Transjugular portography in a patient bleeding from gastric varices. Note that balloon tamponade did not suppress fundal varices filling.

trial has shown that TIPS is more efficient than cyanoacrylate in prevention of rebleeding (secondary prophylaxis) from large gastric varices [87]. This interesting finding must be confirmed by other groups and after a long-term followup. It should be mentioned that due to the large size of fundal varices, the risk of rupture is still present even at a low portacaval gradient (<12 mmHg) after TIPS [88, 89]. This is probably best explained by the relationship between the variceal tension (and therefore the risk of rupture) and the variceal size. For this reason, it is now recommended to embolize gastric varices at the time of TIPS placement [90] (Figures 5 and 6).

**5.1.5. Ectopic Varices.** Varices may develop anywhere along the digestive tract in patients with portal hypertension (duodenum, jejunum, colon, rectum, stomies) and may bleed. Local treatments are either impossible or associated with a high rate of rebleeding. The best approach is the TIPS procedure, which can be combined with embolization of the varices [91, 92] (Figure 7).

**5.1.6. Portal Hypertensive Gastropathy.** These gastric lesions rarely induce problematic bleeding. Anecdotal case reports suggest that TIPS may control bleeding in these patients [93].

**5.1.7. Gastric Antral Vascular Ectasia (GAVE).** Chronic bleeding from GAVE may be difficult to manage. However, TIPS does not help to control haemorrhage, probably because these vascular lesions are related to liver disease and not to portal hypertension [93–95].

TABLE 6: Comparison of TIPS and large volume paracentesis in the treatment of refractory ascites (from D'Amico et al. [96]).

Treatment	Number of patients	Recurrence of ascites $n$ (%)	Encephalopathy $n$ (%)	Mortality $n$ (%)
TIPS	149	66 (44%)	72 (48%)	69 (46%)
Paracentesis	156	135 (87%)	51 (33%)	82 (54%)



FIGURE 6: Embolisation of fundal varices using an Amplatzer® vascular plug, in conjunction with the TIPS procedure due to persistence of fundal varices filling despite a functional TIPS.

**5.2. Ascites.** Ascites is a frequent complication of portal hypertension. It may become resistant to medical treatment in nearly 5–10% of cases [97], and the TIPS procedure has been evaluated for this situation in case series [98–100] and several prospective randomized controlled trials [101–106]. TIPS-induced decrease in portal pressure leads to a good control of ascites in a majority of cases and more often than repeated large volume paracentesis. However, hepatic encephalopathy is observed more frequently, and survival is not improved in a majority of trials [96, 107, 108] (Table 6). However, a recent meta-analysis showed different results after analysing individual data [109]. Moreover, a recent study demonstrated that survival was better in the TIPS group as compared to the paracentesis group; it should be mentioned that in this study, the patients had good liver and renal function [103]. Therefore, this issue is still controversial. There is no clinical controlled trial on the long-term efficacy of PTFE-covered stents in the treatment of refractory ascites. It is now agreed that TIPS may be offered to cirrhotic patients with moderately impaired liver function, without organic kidney disease and preferably in younger patients (less than 65 years) [1]. Liver transplantation should be considered as a backup in case of TIPS failure [110]. The quality of life must be also be considered in the decision making process [111] if transplantation is not an option.

**5.3. Pleural Effusion.** This is an equivalent of ascites, but the tolerance is poor as only a limited amount of fluid in the pleural may induce disabling dyspnea. Repeated pleuracentesis is risky and chronic drainage is often associated with infection of the fluid. TIPS is a good option, but the risks of

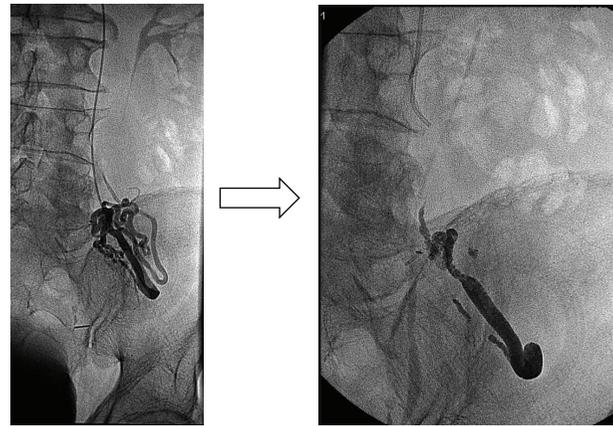


FIGURE 7: (a) Stomal varices in a patient with cirrhosis and colostomy. (b) Treatment of stomal varices with TIPS and embolization using histoacryl injections.

severe hepatic encephalopathy and/or liver failure following TIPS are similar to that observed in ascitic patients [112–114].

**5.4. Hepatorenal Syndrome.** The chronic form of functional renal failure associated with ascites (hepatorenal syndrome type 2) is usually reversible after TIPS; by contrast, hepatorenal syndrome type 1 which is progressive, more severe, and associated with progressive liver failure usually responds less well as TIPS may aggravate the liver insufficiency [115–117]. It has no role in these patients except for highly selected cases as a bridge to liver transplantation.

**5.5. Budd Chiari Syndrome.** The management of this syndrome includes diuretic therapy and chronic anticoagulation. In refractory cases, surgical side-to-side portacaval shunt has been used in the past but is no longer used due to the operative risks and the conflicting results [118]. TIPS, which is a nonsurgical equivalent, has been widely tested and demonstrated promising results (control of ascites, reversal of liver failure) in large series [119, 120]; however, the technique of TIPS placement is difficult given the absence of hepatic veins and the caudate lobe hypertrophy (Figures 8, 9 and 10). These patients must be anticoagulated life long. There is no controlled trial comparing TIPS with liver transplantation, but the good results observed after TIPS justify its use first, transplantation being considered in TIPS failure.

**5.6. Veno-Occlusive Disease.** Several case reports have evaluated the TIPS procedure in the treatment of veno-occlusive disease with some good results [121, 122].

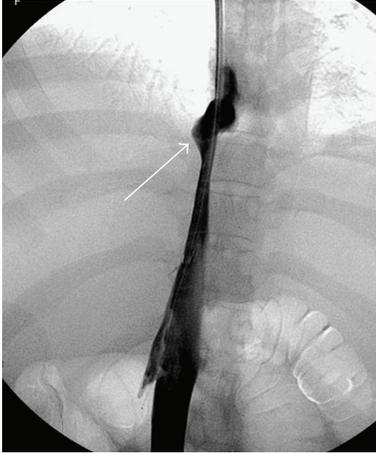


FIGURE 8: Cavography in a patient with Budd Chiari syndrome. Note that the right hepatic vein was almost completely occluded (arrow).



FIGURE 9: Transjugular portography in the same patient.

### 5.7. Miscellaneous Indications

**5.7.1. Preoperative TIPS.** It has been suggested that relief of portal hypertension before abdominal surgery in cirrhotic patients could decrease the perioperative bleeding and post-operative complications, such as, ascitic leak [123]. However, TIPS-associated complications are not infrequent [124]; the best candidates for preoperative TIPS are cirrhotic patients with well-preserved or moderately impaired liver function (Pugh class A or B) and a significant amount of venous collaterals in the operative area. It should also be mentioned that preoperative TIPS would prevent the formation of stomal varices after surgery, which often induce recurrent bleeding (Figure 7).

**5.7.2. Hepatopulmonary Syndrome.** A recent review reports 6 cases of hepatopulmonary syndrome with an improvement in oxygenation after TIPS placement in 5 patients [125–127]. The rationale of this approach is difficult to understand as worsening of vasodilatation usually follows the TIPS

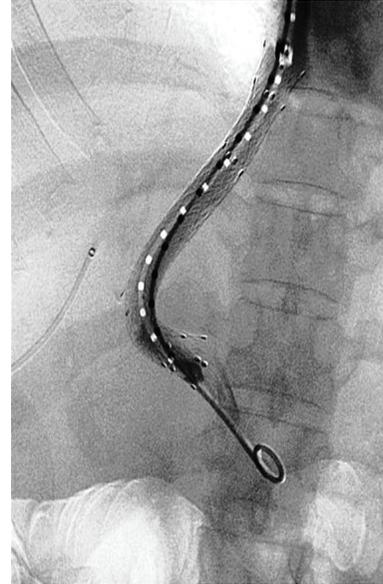


FIGURE 10: Successful TIPS placement after portal vein catheterization by a transjugular approach.

procedure, which could aggravate hypoxemia. Therefore, the mechanism of action is unknown.

## 6. The TIPS Unit

Experience with this procedure over last 20 years clearly demonstrates the need for a multidisciplinary approach. First of all, the indications for TIPS should be discussed rigorously according to a risk benefit approach; preoperative evaluation should include not only the liver function parameters, the cardiac function, but also the assessment of the comorbidities and the evaluation of the risks of post-TIPS chronic encephalopathy. The benefits of TIPS implantation must be weighed against that of liver transplantation. Therefore, hepatologists (or gastroenterologists), cardiologists, interventional radiologists, intensive care specialists, and transplant surgeons play a role in the decision making process. Primary patency higher than 90% after the TIPS placement is a prerequisite in such a TIPS unit. Followup is also crucial as post-TIPS complications may occur and must be treated. Ideally, these patients must be followed regularly in a specialized TIPS clinic, and the surveillance of the TIPS function as well as screening for hepatocarcinoma is mandatory. The collaboration of a highly trained nurse is essential.

## 7. Conclusions

The TIPS procedure is now a well-established treatment of complications of portal hypertension. Technical advances and well-designed clinical studies provide a scientific basis to define the best indications. Cost effectiveness analysis must be done in the future taking into account recent developments (technical improvements, better selection of patients, and better management after TIPS). However,

severe complications still exist and have to be addressed as stated in a recent editorial [128].

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## Review Article

# Endoscopic Management of Portal Hypertension

Said A. Al-Busafi,<sup>1,2</sup> Peter Ghali,<sup>1</sup> Philip Wong,<sup>1</sup> and Marc Deschenes<sup>1</sup>

<sup>1</sup> Hepatology Unit, Division of Gastroenterology, Royal Victoria Hospital, McGill University Health Center, Montreal, QC, Canada H3A 1A1

<sup>2</sup> Gastroenterology and Hepatology Unit, Department of Medicine, College of Medicine and Health Sciences, Sultan Qaboos University, P.O. Box 35, 123 Muscat, Oman

Correspondence should be addressed to Said A. Al-Busafi, busafis@squ.edu.om

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Cirrhosis is the leading cause of portal hypertension worldwide, with the development of bleeding gastroesophageal varices being one of the most life-threatening consequences. Endoscopy plays an indispensable role in the diagnosis, staging, and prophylactic or active management of varices. With the expected future refinements in endoscopic technology, capsule endoscopy may one day replace traditional gastroscopy as a diagnostic modality, whereas endoscopic ultrasound may more precisely guide interventional therapy for gastric varices.

## 1. Introduction

The most common cause of portal hypertension (PH) is liver cirrhosis, and this term was first introduced by Gilbert and Carnot in 1902 to describe a clinical entity characterized by ascites, splenomegaly, and variceal bleeding [1]. The development of PH in cirrhosis marks a milestone in the natural history of the disease as its complications range from the development of gastroesophageal (GE) varices with or without bleeding, ascites, hepatorenal syndrome, and hepatic encephalopathy. The hepatic venous pressure gradient (HVPG), measured as the difference between the wedged (portal vein) and the free hepatic venous pressures (inferior vena cava), becomes increased over the normal value of 5 mmHg, and is associated with variceal bleeding when elevated above 12 mmHg [2]. Varices are common in patients with cirrhosis (30% and 60% of patients with compensated and decompensated cirrhosis, resp.) [3], and if left untreated, are associated with bleeding in approximately 10% and 30% at 2 years in patients with small and large varices, respectively.

Variceal bleeding is a significant cause of morbidity and mortality worldwide [3]. Despite technical and clinical advances achieved in the last 3 decades, variceal bleeding

still carries a mortality of up to 15–20% at 6 weeks with each episode (ranges from 0% in Child-Pugh class A to 32% in Child-Pugh class C) [4, 5]. Nonetheless, there have been recent improvements in survival following variceal bleeding [6], attributable to advances in resuscitation and critical care, pharmacologic therapy and endoscopic treatment.

## 2. Pathophysiology of Variceal Formation and Rupture

Variceal bleeding is the final result of a chain of events initiated by an increase in portal pressure, followed by the development of varices and subsequent progressive dilation of these varices until they rupture and bleed. The portal system and the systemic venous circulation are connected at several locations [7], with GE collaterals being the most frequent and clinically relevant. The appearance of varices in patients with compensated cirrhosis marks the transition from clinical stage 1 (1% risk of death per year) to stage 2 chronic liver disease (3.4% risk of death per year) [3]. At this juncture, the HVPG increases to more than 10 mmHg.

Variceal rupture is governed by Laplace's Law and is the end result of increasing the variceal pressure, with

increased diameter of the varices and increased wall tension with reduced wall thickness [8]. The variceal wall thickness can be evaluated visually as the presence of red wale markings, reflecting areas where it is especially thin [9, 10], and is more often found with advanced Child-Pugh class. Many studies have shown that variceal bleeding does not occur if HVPG is reduced to below 12 mmHg [11].

Variceal rupture often occurs at the level of the GE junction where the varices are very superficial and thus have thinner walls [12]. In addition, the transmural pressure of the esophageal varices (EVs) is higher than in varices at other locations due to the negative esophageal luminal pressure during inspiration, resulting in higher wall tension, and risk of rupture.

### 3. Role of Endoscopy in the Diagnosis and Grading of Varices

Varices should be sought in all patients with clinical suspicion of cirrhosis, especially if they have stigmata of chronic liver diseases for example, spider nevi, palmar erythema, splenomegaly, and ascites. Although varices can be detected using various diagnostic and imaging techniques such as ultrasound, CT, and MRI scanning, they are less precise than endoscopy.

**3.1. Esophagogastroduodenoscopy (EGD).** EGD is considered the gold standard for the diagnosis of GE varices [13]. Direct visualization is needed to assess the size and presence of high-risk stigmata of bleeding, in order to decide if prophylactic variceal banding is warranted. Examination for EV is best done during withdrawal of the scope, with the esophagus maximally insufflated with air and the stomach completely deflated in order to avoid any mucosal folds which can be interpreted as varices. GVs are generally described according to the Sarin classification and the presence or absence of red wale signs (Figure 1) [13]. EVs are usually described as in the lower, middle, or upper esophagus, and graded as small (<5 mm) or large (>5 mm) with the latter encompassing medium-sized varices when 3 grades are used (small, medium, and large) [13]. In addition, the presence of high-risk stigmata of bleeding, that is, red color signs (red wale sign and cherry red spots) must be noted.

**3.2. Endoscopic Ultrasound (EUS).** Vascular changes within the esophagus, gastric or rectal walls can be accurately confirmed with EUS [14], but currently this modality has a limited role in clinical practice. EUS appears to perform as well as EGD for detection of clinically significant EVs [15], but is superior to EGD for detection of GV [16]. The diagnosis of GV is probably the most important clinical application of EUS in patients with PH [17], but potentially could be used to determine predictors for recurrence of varices after endoscopic obliteration, by assessing for the presence and size of paraesophageal veins [17]. EUS has no role in grading the size of esophageal varices, but in selected cases, may

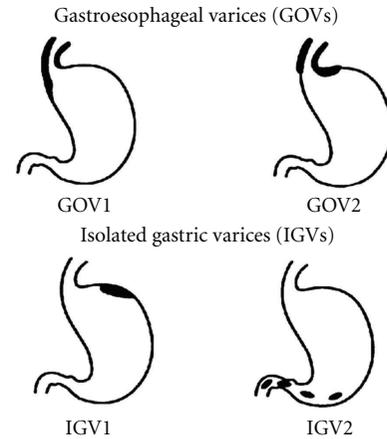


FIGURE 1: Sarin Classification of gastric varices (adapted from Sarin et al. [69]).

be of help in guiding endoscopic therapy [17–19]. Future applications may include EUS-guided direct measurement of portal pressure and transjugular intrahepatic portosystemic shunt (TIPS) placement, but to date, safety data are lacking [17].

**3.3. Capsule Endoscopy (CE).** Current guidelines recommend screening patients with cirrhosis with EGD to detect varices [13, 20]. However, the need for sedation and invasive nature of EGD may limit acceptability by patients and adherence to screening programs [21]. Two different types of CE have been available for the evaluation of patients with portal hypertension: esophageal CE and small bowel CE. The main advantage of these diagnostic tools is that they are relatively less invasive, potentially increasing patient acceptability and adherence to screening/surveillance programs.

When esophageal CE has been compared with EGD, its performance in recognizing the presence and the size of EVs was good, but results have varied greatly across studies, and better designed trials are needed [21]. Esophageal CE has some limitations related to cost, absence of a reliable variceal size grading system, and need for specialized equipment. Currently, it can only be recommended in patients unable or unwilling to have an EGD [22]. In other studies for portal hypertensive gastropathy (PHG), esophageal CE showed sensitivity (from 74%–100%) and specificity (from 17%–83%) [22] when compared to EGD.

In the past few years, several studies have been published concerning the use of small bowel CE for detection of portal hypertensive enteropathy (PHE). The prevalence of PHE is higher than previously reported [22], but its role in causing chronic blood loss or anemia remains uncertain. CE was able to identify potential sources of bleeding in 89.5% of patients and active bleeding sites in 15.8%. Based on these findings, small bowel CE could have diagnostic utility in patients with PH and chronic anemia to identify obscure sources of bleeding [22, 23].

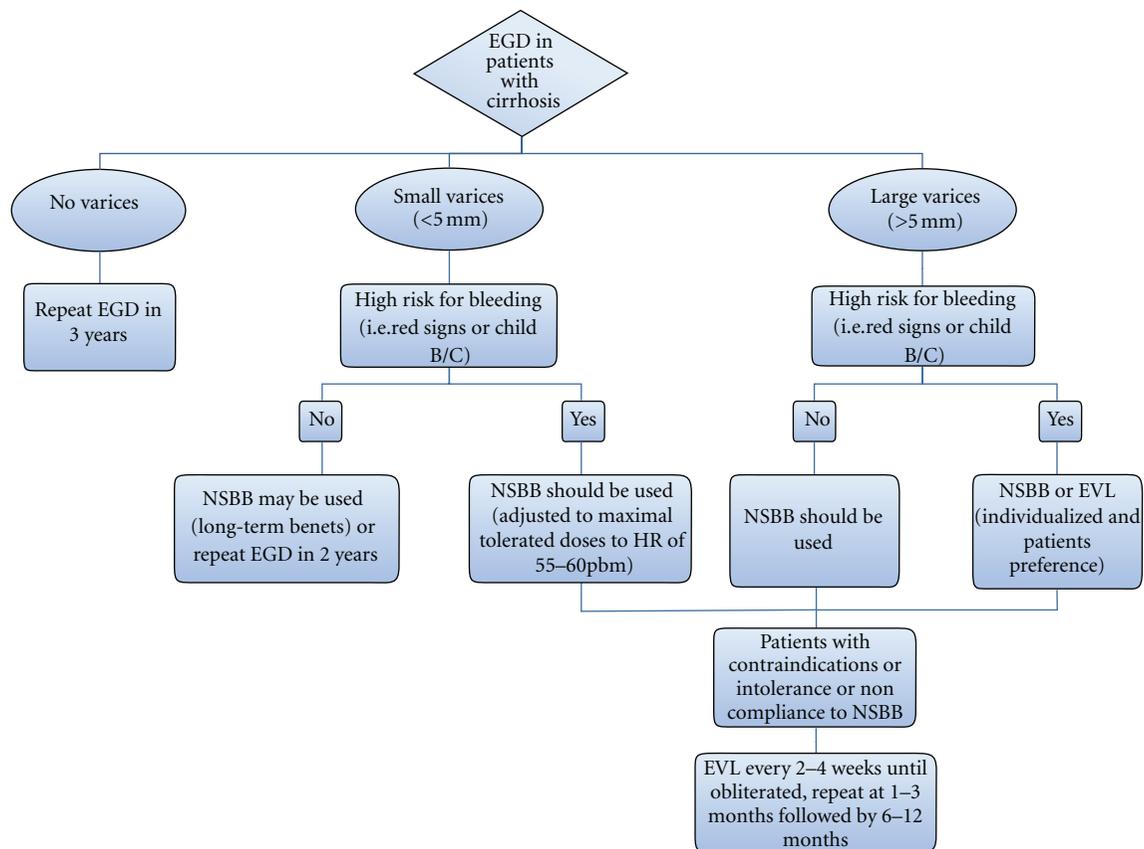


FIGURE 2: Algorithm for screening for esophageal varices and primary prophylaxis of variceal bleeding in cirrhotic patients. EGD indicates esophagogastroduodenal endoscopy; NSBB: nonselective beta blockers; EVL: endoscopic variceal ligation; HR: heart rate.

#### 4. Role of Endoscopy in Primary Prophylaxis of Variceal Bleeding

The reported risk of bleeding from GE varices in patients with cirrhosis at 1 year varies widely (ranges from 6%–76%) [10], likely reflecting the heterogeneity of the patient population. Therefore, it is important to perform EGD to identify high-risk patients who could benefit from prophylaxis for first variceal bleeding (Figure 2).

Debate exists between a pharmacologic or endoscopic approach as the best method of primary prophylaxis [13, 24]. Pharmacotherapy consists of nonselective beta blockers (NSBBs), which have systemic effects to reduce portal pressure, whereas endoscopic therapy with endoscopic variceal ligation (EVL) acts locally and has no effect on portal pressure or its evolution. Endoscopic sclerotherapy (ES) has generally been abandoned because of inconsistency of results across trials and higher morbidity and mortality than EVL [13, 24, 25].

Both NSBB and EVL are superior to no treatment for the prevention of a first variceal hemorrhage. NSBB are indicated in patients with cirrhosis and small EV with high-risk criteria for bleeding (presence of red signs or CPC B/C). In contrast, their long-term benefit in other patients with small varices has not been established [13, 24]. NSBBs or EVL as first-line therapy for primary prophylaxis of

bleeding in patients with cirrhosis and large EVs with or without high-risk criteria for bleeding has been the subject of several meta-analyses [24] (Figure 2). Both modalities are effective in minimizing the risk of a first bleeding episode in patients with cirrhosis and large EV, independently of the presence of red signs. Some data suggest that EVL may be more effective in preventing first bleeding [24, 26] and is more acceptable by physicians and patients [27], but there is no benefit with regard to mortality and carries with it procedure-related complications [26]. Moreover, EVL is more expensive, requires specialized staff and cannot prevent bleeding from PHG. In contrast, NSBBs are effective, cheap, and have a more favorable safety profile. Furthermore, NSBB might have a potentially favorable effect on other PH-related complications such as spontaneous bacterial peritonitis (SBP) [24, 28].

NSBBs are the therapy of choice in patients with large EVs with no high-risk criteria for bleeding, and EVL should be considered in patients with contraindications, intolerance or noncompliance to NSBB [13].

The routine use of NSBB in patients with advanced cirrhosis has been called into question based upon a prospective study of 151 patients with cirrhosis and refractory ascites [29]. Median survival was significantly longer in patients who did not receive propranolol versus those who did (20 versus 5 months). However, more studies are needed to

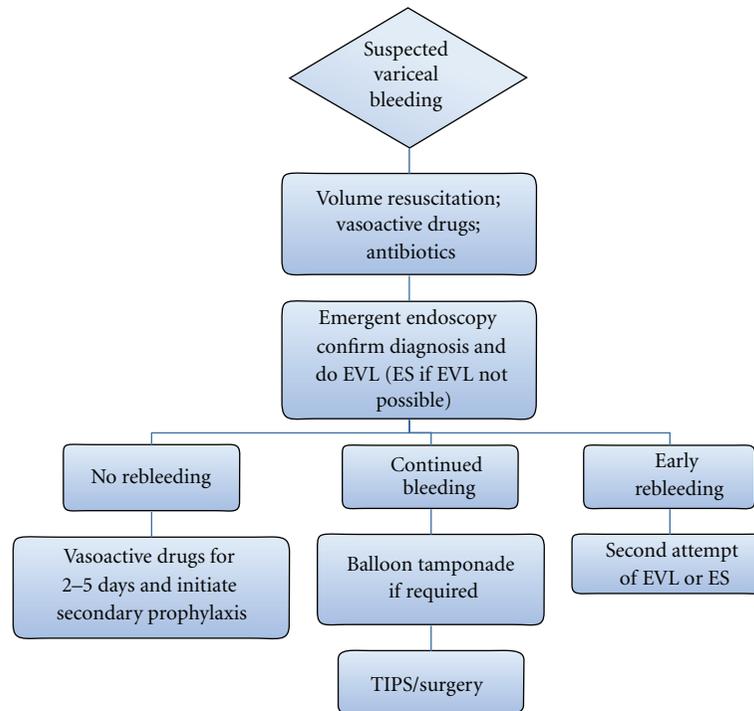


FIGURE 3: Algorithm for management of acute variceal bleeding. EVL indicates endoscopic variceal ligation; ES: endoscopic sclerotherapy; TIPS: transjugular intrahepatic portosystemic shunt.

establish if NSBB exert different effects on different subsets of patients with cirrhosis. While waiting for the results of such studies, patients with ascites who are on NSBB should be monitored closely, and consideration should be given to discontinuing NSBB when either sepsis or HRS develop [30].

In addition to ES, other approaches to primary prophylaxis that are not recommended include nitrates (either alone or in combination with NSBB), shunt therapy, and combination therapy with NSBB and EVL [13, 20].

Based on the current evidence, EGD surveillance is recommended in patients with no varices (every 3 years) or with small varices not receiving prophylaxis (every 1-2 years), in order to detect newly formed large varices [13]. Patients with decompensated cirrhosis should have EGD at the time of diagnosis and annually thereafter. Routine follow-up EGD is not necessary for patients who receive NSBB but may be performed when clinical picture dictates.

## 5. Endoscopic Management of Acute Variceal Bleeding (AVB)

Acute variceal bleeding in patients with cirrhosis indicates decompensation and a high-risk of death [3]. Management of AVB should aim both at controlling bleeding and at preventing early rebleeding, which is particularly common within the first week and is associated with increased mortality [31]. The management of the AVB is a multistep process that includes the initial assessment of the patient, effective resuscitation, timely diagnosis, control of bleeding, and prevention of early rebleeding and complications such as

infection, hepatorenal syndrome, or hepatic encephalopathy. Complicated cases may require a multidisciplinary approach involving a gastroenterologist, intensivist, general surgeon and interventional radiologist. It has been previously shown that about two-thirds of deaths in which bleeding is the precipitating cause occur within 24 hours of the onset of bleeding, thus emphasizing the need to act quickly and decisively as soon as the patient reaches the hospital [32].

The initial management includes appropriate volume resuscitation, blood transfusion to keep hemoglobin levels approximately 80 g/L, antibiotic prophylaxis, and endotracheal intubation in selected cases (Figure 3) [13]. Vasoactive drugs (terlipressin; somatostatin or its analogues octreotide and vapreotide) should be initiated as soon as variceal bleeding is suspected and continued for up to 5 days after diagnosis is confirmed [13].

Emergency EGD, performed within the first 12 hours of admission, is one of the cornerstones of management as it confirms diagnosis and is therapeutic. It is known that about 25–30% of bleeds in cirrhotic patients are of nonvariceal origin, mainly peptic ulcer and PHG [8]. In addition, when endoscopy is done early, active bleeding is found in 39–44% of patients, with 33–44% showing signs of recent bleeding (clots or “white nipple” on varices) [33], but no sign of active or recent hemorrhage in the remaining 12–28% [8]. There are 2 endoscopic methods available for AVB: endoscopic sclerotherapy (ES) and endoscopic variceal ligation (EVL).

*Endoscopic Sclerotherapy (ES).* ES was first described in 1938 by Crafford and Frenckner using operative rigid endoscopes

with patients under general anesthesia [34]. Currently, ES is relatively easy to perform by fiberoptic endoscopy using flexible catheters with a short needle tip (23 or 25 gauge). Sclerosants are injected into the variceal lumen (intravariceal) or adjacent to it (paravariceal) with rapid thrombus formation. Both intravariceal and paravariceal injections have been associated with equally good outcomes [35]. The outcomes are also similar regardless of the type of sclerosant used [36], the volume injected, or frequency of sessions [37].

Compared to EVL, the advantages of ES are its ease of use, quick assembly, and lack of a need to withdraw and reinsert the endoscope. However, ES is associated with more complications than EVL, such as chest pain, fever, dysphagia, pleural effusion, and perforation [38, 39]. Rarer complications include esophageal strictures, mediastinitis, chylothous effusion, pneumonia and bacteremia leading to SBP and distal abscesses [38, 40]. Esophageal ulcers are common and may cause bleeding in 20% of patients [38]. A recent Cochrane meta-analysis showed that ES was not superior to the vasoactive drugs in terms of control of bleeding, rebleeding, and mortality [41].

*Endoscopic Variceal Ligation (EVL).* The first reports of EVL appeared in 1988 by Stiegmann et al. [42], and the procedure was developed as an alternative to ES for treatment of AVB. The introduction of multiband devices, which allow the placement of 4–10 bands at a time, has made the technique easier to perform, avoiding the use of overtubes and their related complications. Endoscopic variceal ligation causes occlusion of the varix and then thrombosis with ischemic necrosis of the mucosa. When the bands fall off a few days later, a superficial ulceration is left which eventually scars [43], making subsequent redevelopment of varices more difficult. Compared to ES, a meta-analysis of 7 randomized controlled trials (RCTs) showed a tendency toward benefit of EVL in the initial control of bleeding, recurrent bleeding, side effects, need for fewer endoscopic treatments, and survival [39]. Interestingly, HVPg transiently decreases after EVL, while it increases after ES [44]. Therefore, EVL has become the treatment of choice for AVB, although ES can be used in patients in whom EVL is technically difficult, for example, in treating patients with AVB where there is marked difficulty in visualizing the mucosa [13, 20].

Complications of EVL include chest pain and transient dysphagia which are common and respond well to oral analgesia and oral antacids. Superficial esophageal ulcers are frequent, but seldom bleed. Other potential complications such as massive bleeding from variceal rupture, esophageal perforation, and esophageal strictures [45] are fortunately rare. Additionally, EVL may cause worsening of and/or appearance of PHG [46].

*Combination Therapy.* Combination of vasoactive drugs plus EVL has been proposed as the standard of care for AVB [13, 20]. A meta-analysis of 8 trials involving 939 patients demonstrated that compared to endoscopic therapy alone (ES or EVL), endoscopic and vasoactive

drugs (octreotide, somatostatin, or vapreotide) therapy improved the initial control of bleeding and 5-day hemostasis without differences in severe side effects or mortality [47].

Other studies have looked at combining EVL and ES in order to speed variceal eradication, reduce the likelihood of rebleeding [48], and reduce the incidence of recurrent varices [49]. A meta-analysis of 7 RCTs by Singh et al. noted that combination therapy offered no advantage over EVL alone in the control of bleeding varices, prevention of rebleeding or reducing mortality [50]. In addition, a significantly higher incidence of esophageal stricture was seen with combination therapy. Several variations in the types of sclerosants and the protocol for administering ES in combination with EVL have been described [51, 52].

Data on other combination therapies including EVL with thermal therapies either argon plasma coagulation (APC) [53–55] or microwave cautery are emerging [56]. However, none of these techniques has been sufficiently studied to be recommended in routine clinical practice.

*Failures of Endoscopic Therapy.* Treatment failure is defined as a failure to control AVB within 24 hours, or failure to prevent clinically significant rebleeding or death within 5 days of treatment [20]. The current first-line therapy, that is, pharmacologic and endoscopic, fails to control bleeding in approximately 10–15% of patients [8, 13]. These patients are at high-risk for exsanguinating and other complications related to active bleeding. Child-Pugh class, shock at admission, presence of portal vein thrombosis, active bleeding at endoscopy, and elevated HVPg >20 mmHg have been shown to be predictive of treatment failure [8, 57].

Although a post hoc analysis of a RCT suggested that a higher dose of somatostatin (500 µg/h) had significantly higher control of bleeding and better survival [48], this finding awaits confirmation by trials. A second attempt at endoscopic therapy using EVL or ES can be performed in more stable patients, for example, EVL in patients who failed ES [58]. If this is unsuccessful, more definitive therapy must be instituted with shunt therapy (surgical or TIPS)[13]. Indeed a recent RCT showed that early use of TIPS (i.e., within 72 hours after admission) in patients with AVB and at high-risk for treatment failure (i.e., Child-Pugh class C cirrhosis (a score of 10 to 13) or class B disease (a score of 7 to 9) with active variceal bleeding) was associated with significant reductions in treatment failure and in mortality [59].

Balloon tamponade can also be used in patients who failed in initial endoscopic therapy to obtain temporary hemostasis (maximum 24 hours) while preparing for more definitive therapy. Preliminary studies have described the placement of self-expanding metallic stents as an alternative to balloon tamponade for the control of refractory variceal hemorrhage [60, 61]. In these studies, the stents had a high success rate with minor complications. However, these findings must be confirmed in well-designed trials before use in clinical practice.

## 6. Role of Endoscopy in Secondary Prophylaxis of EV Bleeding

Once AVB is successfully controlled, rebleeding may occur in approximately 60% of patients if preventive measures are not taken [13]. It is, therefore, essential that patients, who survive an episode of AVB, should receive secondary prophylaxis to improve survival. The approaches recommended include NSBB, EVL, TIPS, shunt surgery, and liver transplantation [13, 20]. Combined approaches with NSBB plus EVL are considered the best option for secondary prophylaxis of variceal hemorrhage [62, 63]. In patients who are not candidates for EVL, the strategy would be to maximize portal-pressure reduction by combining NSBB plus nitrates [5]. Shunt operations or TIPS are reserved for endoscopic and medical failures [13, 20].

ES has been largely replaced by EVL and should no longer be used in the secondary prophylaxis of variceal bleeding [13]. A meta-analysis of 7 trials showed that, compared with ES, EVL reduced the rebleeding rate (odds ratio 0.46), the mortality rate (odds ratio 0.67), the rate of death due to rebleeding (odds ratio 0.49), and the development of esophageal strictures (odds ratio 0.1) [39]. Variceal obliteration was achieved in similar proportions with both techniques, but the number of treatments necessary to achieve obliteration was lower with EVL.

Combination of EVL with other endoscopic modalities to manage EVs has been a focus of research for gastroenterologists. Studies evaluating different approaches have produced heterogeneous results. Considering the available data, it appears that the addition of ES [64–66], microwaves [67], or APC [55] following variceal obliteration achieved by EVL could effectively reduce variceal recurrence. However, controlled trials are needed before they can be routinely recommended. In contrast to these findings, most studies using synchronous combination of EVL and ES during initial variceal obliteration have demonstrated decreased efficacy and a higher complication rate compared with EVL alone [68].

## 7. Endoscopic Management of Gastric Varices (GVs)

Bleeding from GV is fortunately less frequent, but generally more severe than bleeding from EV and may be technically difficult to treat [69]. In GV, the blood flow is relatively increased, and so the bleeding is often rapid and torrential. Although prospective RCTs in successful endoscopic hemostasis and obliteration of GV using different agents and techniques with improved outcome of GV bleeds have been reported, no consensus has been reached on the optimal therapy [70]. The problem is that heterogeneous types of GV including GOV1 in more than 50% subjects have been included in these trials without definite explanation or classification of the varices, making it difficult to compare with studies [70–72].

The endoscopic treatment modalities largely depend on the type of the GV (Figure 4). The Sarin classification, which

categorizes GV based on their location in the stomach and their relationship with EV, is most widely used (Figure 1) [20, 69].

*Control of Acute GV Bleeding.* The literature on the endoscopic management of GV bleeding is not as clear as that for EV. Gastroesophageal varices type 1 (GOV1) constitute an extension of esophageal varices along the lesser curvature of the stomach. Therefore, they should be managed in the same way as EV. In addition, the GOV1 bleeding, hemostasis and rebleeding rate are similar to those of EV [73]. Currently, there are limited data regarding the management of bleeding from fundal varices (gastroesophageal varices type 2 (GOV2) or isolated gastric varices type 1 (IGV1)). An exception is IGV1 which are secondary to isolated splenic vein thrombosis, in which therapy consists of splenectomy. There are various endoscopic techniques of treatment for fundal varices including, ES, EVL, gastric variceal obliteration (GVO) with glue, and thrombin injection.

Compared to its efficacy for treatment of GOV1 bleeding, ES was shown by a number of studies to be ineffective for patients with fundal varices because of low rate of primary hemostasis, high rate of rebleeding and high incidence of local complications, for example, perforation and ulcer formation [70]. The reason is that there is a high volume of blood flow through GV compared to EV, resulting in the rapid escape of sclerosant into the systemic circulation.

Compared to ES or EVL, GVO with a tissue adhesive (polymers of cyanoacrylate) is more effective for acute fundal GV bleeding with a better rate of controlling the initial hemorrhage as well as lower rebleeding rate [70–72, 74–76]. Therefore, cyanoacrylate is recommended as the preferred treatment for control of bleeding from fundal GV, where it is available and with appropriate expertise [13, 20]. In the United States, it is used only in a few centers under research protocols, and its use is not approved by the United States Food and Drug Administration.

When introduced into the varix and upon contact with blood, cyanoacrylate immediately polymerizes into a firm clot leading to obliteration of the varix. Complications from cyanoacrylate injection are rare, and these include rebleeding due to extrusion of the glue cast (4.4%), sepsis (1.3%), distant emboli (pulmonary, cerebral, and splenic; 0.7%), gastric ulcer formation (0.1%), major GV bleeding (0.1%), and mesenteric hematoma associated with hemoperitoneum and bacterial peritonitis (0.1%). The complication-related mortality rate is approximately 0.5% [77]. In addition, cyanoacrylate can also be used as secondary prophylaxis for GV bleeding. In one trial, cyanoacrylate was more effective than NSBB for the prevention of rebleeding and improved survival during a median followup of 26 months [78].

The evidence for efficacy of EVL for treatment of bleeding GVs is mixed because most of the studies used small sample sizes and had predominantly patients with GOV1 or 2 [70]. However, a relatively large RCT with 2 years of followup and a greater proportion of IGV1 patients, comparing GVO with cyanoacrylate glue versus EVL in cirrhotics with acute GV bleeding, showed that both treatment arms were similar

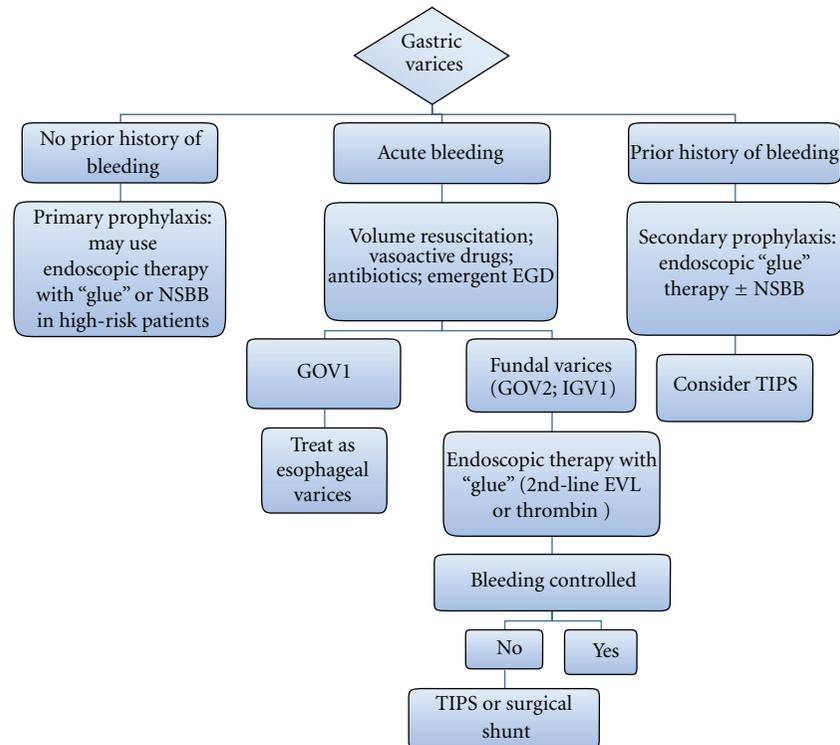


FIGURE 4: Algorithm for endoscopic management of gastric varices. NSBB indicates nonselective beta blockers; EGD: esophagogastro-duodenal endoscopy; GOV: gastroesophageal varices; IGV: isolated gastric varices; EVL: endoscopic variceal ligation; TIPS: transjugular intrahepatic portosystemic shunt.

in controlling active bleeding but rebleeding was higher in EVL group [71]. Therefore, EVL is recommended to be used as an alternative option, where tissue adhesives are not available [13]. Another study has shown the successful use of elastic bands and detachable snares in controlling acute rebleeding and achieving gastric variceal eradication [79], but the cumulative variceal recurrence rate was 100% at 2 years.

Another promising alternative endoscopic therapeutic agent is the intravariceal injection of thrombin [70, 80–82]. Thrombin has not been subjected to controlled trials, but the available data have suggested its usefulness in achieving excellent initial hemostasis and in being easy and very safe to use for control of GV bleeding [70]. Further controlled trials are required before it can be universally recommended. TIPS should be considered if endoscopic therapy is not possible or after a single failure of endoscopic treatment [13].

*Primary Prophylaxis for GV Bleeding.* There are limited data on primary prophylaxis of GV bleeding [20]. In a recently published well-designed RCT with large sample size and median followup of 26 months, cyanoacrylate was found to be more effective than NSBB therapy in preventing first GV bleeding and also to improve survival in patients with high-risk GVs (GOV2 and IGV1) [83]. High-risk factors for first bleeding from GVs were of size GV >20 mm, MELD score  $\geq 17$ , and the presence of PHG.

## 8. Endoscopic Management of PHG and GAVE

The mucosal changes in the stomach of patients with PH which may present with bleeding include PHG and gastric antral vascular ectasia (GAVE). These are 2 clearly distinct clinical entities with different pathophysiology, endoscopic appearance, and treatment. Portal hypertensive gastropathy, as its name indicates, is associated with PH, whereas GAVE is also found in patients without PH or liver disease. Liver failure appears to play a role in the development of GAVE but has been shown to resolve after liver transplantation [84]. PHG is typically located in the proximal stomach, whereas GAVE is typically located, as its name indicates, in the gastric antrum. PHG is primarily an endoscopic diagnosis based on the presence of red spots on a background of snakeskin mosaic pattern, whereas GAVE is endoscopically characterized by the presence of red spots without a background mosaic pattern [20].

The management of PHG is based on measures that reduce portal pressure, namely, the use of octreotide in the acute setting [85] and NSBB with iron therapy in chronic blood loss [86]. TIPS should be considered as salvage therapy in patients with recurrent bleeding despite pharmacological therapy [87]. Only one single center study of 29 patients (11 patients with PHG) has evaluated the use of endoscopic therapy of PHG with APC [88]. The APC was successful in managing bleeding and reducing transfusion requirement in this group of patients. The data are limited, and this endoscopic approach needs further evaluation by RCT, but

it could be considered in patients who are transfusion-dependent in spite of NSBB and those who are not candidate for TIPS.

Specific measures to treat patients with bleeding GAVE are substantially different from those used in PHG. It does not respond to portal pressure reducing therapies, such as TIPS or shunt surgery. The mainstay of therapy in GAVE is the endoscopic ablation of the lesions. There are different endoscopic therapeutic methods which have been used in the setting of GAVE including APC, heater probe, gold probe, cryotherapy, band ligation, and laser therapy [89]. Most studies evaluating the use of APC have reported good results [88–90]. APC, which produces thermal coagulation by applying contact with mucosa, is easy to use and the risk of perforation is much lower than with laser therapy. Complications associated with this method are gastric outlet obstruction [91] and the formation of hyperplastic polyps [92]. The sessions should be repeated every 2 to 6 weeks as needed.

Other studies have evaluated the use of different drugs for example, estrogen-progesterone, thalidomide, and surgery with antrectomy, but these should be reserved for when endoscopic therapy has failed. Antrectomy has high morbidity and mortality particularly in patients with decompensated cirrhosis in whom GAVE usually presents.

## 9. Endoscopic Management of Ectopic Varices (EcVs)

Varices occasionally develop at sites other than the stomach and esophagus and come to clinical attention when they bleed. Examples are duodenal, rectal, and peristomal varices. Duodenal varices are the most prevalent and most common cause of bleeding from ectopic varices (EcVs).

Because EcVs are infrequent and account for less than 5% of all PH-related bleeding, there have been no RCTs on the management of this condition, and it is unlikely that there ever will be such a trial. The management is mainly extrapolated from the GE varices literature and a few small studies done in patients with bleeding EcV. Successful outcomes depend on local expertise, location of varices, and the technical feasibility [93]. Initial management involves hemodynamic stabilization, use of vasoactive drugs and antibiotic prophylaxis [13]. Octreotide has been shown to be effective in the control of bleeding colonic varices [94].

Endoscopy is used for both diagnosis and therapy. Most EcVs are within reach of standard endoscopy [95], and for the rest, enteroscopy might be used [96]. ES has been used successfully in controlling bleeding varices in the duodenum [97, 98], rectum [99, 100], and in stomal varices [101, 102]. However, there have been reports of cases of rebleeding of duodenal varices after ES [103], and this is probably a result of the large varices in this area, such that sclerosants fail to concentrate, thereby diminishing the obliterative effects. Cyanoacrylate glue injection has been successfully used to obliterate bleeding duodenal [104, 105], jejunal [106], and rectal varices [107].

EVL for bleeding duodenal varices is challenging because of limited visibility from the banding hood. It may be useful for temporary hemostasis but rebleeding is a problem [108, 109]. However, several cases of successful treatment of rectal varices using EVL have been reported [110, 111].

EUS can be used to better localize and differentiate ECV from other bleeding mucosal lesions [112, 113]. In patients with rectal varices, EUS is a more sensitive diagnostic study than regular endoscopy in detecting early as well as florid changes [114, 115]. Furthermore, EUS can be used to apply a sclerosant or coil embolization when adequate visualization is not possible with conventional endoscopy [116, 117]. EUS is also useful to follow up therapy of the varix after therapy.

## 10. Summary

The development of GE varices is a serious consequence of portal hypertension. Endoscopy plays an indispensable role in the management of varices including diagnosis, staging, preventing first bleeding, control of active bleeding, and preventing rebleeding. This approach has had a positive impact on patient survival. Capsule endoscopy in the future could potentially become an alternative to regular endoscopy for evaluation of the consequences of portal hypertension in the esophagus, stomach, and small bowel. Endoscopic ultrasound can be used to diagnose gastric and ectopic varices as well as to help in guiding endoscopic therapy.

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## Review Article

# Management of Anticoagulation for Portal Vein Thrombosis in Individuals with Cirrhosis: A Systematic Review

**Geneviève Huard and Marc Bilodeau**

*Liver Unit, Hôpital Saint-Luc, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada H2X 3J4*

Correspondence should be addressed to Marc Bilodeau, marc.bilodeau@umontreal.ca

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Non-neoplastic portal vein thrombosis (PVT) is an increasingly recognized complication of liver cirrhosis. It is often diagnosed fortuitously and can be either partial or complete. The clinical significance of PVT is not obvious except in some situations such as when patients are on the waiting list for liver transplantation. The only known therapy is anticoagulation which has been shown to permit the disappearance of thrombosis and to prevent further extension. Anticoagulation is a challenging therapy in individuals with liver cirrhosis because of the well-recognized coagulation abnormalities observed in that setting and because of the increased risk of bleeding, especially from gastrointestinal tract caused by portal hypertension. We herein review the current knowledge on that topic in order to highlight the advantages and disadvantages of the currently proposed therapeutic attitudes in face of the diagnosis of PVT in individuals with cirrhosis.

## 1. Introduction

Nonneoplastic portal vein thrombosis (PVT) is encountered in 0.6 to 26% of individuals with liver cirrhosis [1–4]. The prevalence of PVT increases with the severity of liver disease, being 1% in individuals with compensated cirrhosis and up to 8–25% in candidates for liver transplantation [1, 3–5].

In individuals with cirrhosis, reduced blood flow velocity in the portal vein seems to be the most important local factor responsible for the development of PVT [3, 6]. Several clinical risk factors have been shown to be associated with PVT: they include thrombocytopenia, previous variceal hemorrhage, splenectomy, surgical portosystemic shunt, and endoscopic treatment of esophageal varices [4, 7]. However, instead of being causative, these factors are probably a reflection of the severity of portal hypertension, which is by itself an important risk factor for PVT [4]. More recently, the recognition of a procoagulant imbalance in individuals with advanced liver disease has also been put forward in explaining the development of PVT in this population [1–4, 8]. Indeed, it is now clear that individuals with cirrhosis have a decreased production of liver procoagulant factors (with the exception of factor VIII) and also a decreased production

of anticoagulant factors. The resulting procoagulant imbalance can be demonstrated in particular through the partial resistance to the anticoagulant action of thrombomodulin (a potent activator of protein C). The resistance to thrombomodulin is probably related to the markedly increased plasma levels of factor VIII and the concomitant decrease in protein C levels seen in advanced liver disease [1–4, 8]. Although contradictory results have been reported, a defect in fibrinolysis due to decreased plasma levels of plasminogen and increased levels of plasminogen activator inhibitor could also contribute to the procoagulant imbalance found with cirrhosis [3].

The clinical impact of PVT on liver function is still a matter of great debate in the literature. PVT is a well-known risk factor of early mortality after liver transplantation and can also contraindicate liver transplantation in cases where thrombosis extends to the splenomesenteric confluence [1, 5, 7–9]. PVT is also a predictive factor for mortality, independent of MELD score, in individuals with cirrhosis: the relative risk of death having been shown to be around 2.5 [5, 8, 9]. Because PVT by itself also increases portal hypertension, it increases the risk of variceal bleeding and

has been described to be an independent risk factor for the inability to control variceal bleeding [1, 8, 10]. PVT can also be a life-threatening emergency when thrombosis extends to the superior mesenteric vein in which case it may lead to intestinal infarction [1, 4, 11]. Finally, it has been demonstrated that primary prophylaxis of PVT with low-dose LMWH was effective in reducing mortality and the risk of hepatic decompensation in a cohort of moderately severe cirrhotic individuals (Child B7-C10) [12].

The optimal management of PVT in individuals with cirrhosis is currently not addressed in any consensus publication or practice guidelines [4, 13, 14]. In the present systematic review, we explore the different aspects of the management of PVT in individuals with cirrhosis (excluding cases associated with hepatocellular carcinoma).

## 2. The Benefits of PVT Anticoagulation in Cirrhotic Individuals

To date, only few studies have evaluated the benefits of anticoagulation in individuals with cirrhosis. An obvious goal of anticoagulation is PV recanalization: when cirrhotic individuals with PVT are treated with anticoagulation, complete recanalization has been described in 33–45% while partial PV recanalization is observed in 15–35% of cases [1, 7, 8]. These rates of recanalization are similar to what is described in cases where PVT occurs in noncirrhotic individuals [15].

Senzolo et al. have conducted the largest study published to date on that topic by prospectively enrolling 56 individuals (35 in the treatment group and 21 in the control group) [6]. In the treatment group, 31% had complete PVT and 69% had partial PVT. Thirty-three out of the 35 treated individuals received low molecular weight heparin (LMWH); 2 individuals did not receive anticoagulation because of cavernous transformation. Complete recanalization was achieved in 12/33 (36%) individuals and partial recanalization in 9/33 (27%) individuals, after a mean of  $5.5 \pm 2.6$  months (1–10 months). In univariate analysis, previous bleeding caused by portal hypertension (RR 3.1; CI 1.3–6.9;  $P = 0.01$ ), time between diagnosis and inclusion in the study <6 months (RR 3.5; CI 1.5–8.5;  $P < 0.001$ ), and time between diagnosis and anticoagulation <6 months (RR 3.3; CI 1.2–9.4;  $P = 0.004$ ) were positively associated with PV recanalization. This study also demonstrated that anticoagulation could prevent PVT progression. In the treatment group, 15% of the individuals had progression of their thrombosis compared to 71.4% in the control group ( $P < 0.001$ ).

Another study conducted in Spain by Delgado et al. included 55 cirrhotic individuals with acute/subacute PVT or a progressive splenomesenteric thrombosis [1]. The mean MELD score was 12.8 and thrombosis was partial in 75% of the individuals. In this study, 29 individuals (53%) were treated with vitamin K antagonists (VKA) and 26 individuals (47%) received LMWH. Therapy was administered for a median of 6.3 months and individuals were followed for a median time of 19 months. Complete PV recanalization was achieved in 45% of the cases and partial recanalization

in 15% of the individuals. The only predictive factor for complete PV recanalization in this study was early initiation of anticoagulation after diagnosis (<14 days).

Another important study was conducted by Francoz et al. in 2005 [7]. This case-control study included 29 cirrhotic individuals with PVT on the waiting list for liver transplantation. PVT was partial in 20 individuals (69%) and complete in 9 individuals (31%). Ten individuals (between 1996 and 1998) did not receive anticoagulation therapy and were compared to 19 treated individuals (between 1999 and 2001) who received VKA therapy. In the 10 individuals not receiving therapy, PVT remained stable in 4 individuals and progressed in the other 6. In the 19 treated individuals, complete PV recanalization was achieved in 8 individuals (42%). The difference was statistically significant and in favor of anticoagulation therapy. In this study, there was no evidence that anticoagulation therapy increases blood loss during liver transplantation or that it increases the duration of surgery.

Finally, Amitrano et al. published a study where 28 individuals with PVT were treated with LMWH [11]. PVT was partial in 83% of the cases and 46% of individuals had CHILD B or C cirrhosis. All individuals received enoxaparin 200 U/kg/d for 6 months. After 6 months, the patency of the PV was evaluated and therapy was continued if partial response was demonstrated and was discontinued if complete response or no response to treatment was observed. At 6 months, complete PV recanalization was achieved in 33% of the individuals while partial PV recanalization was achieved in 50%. In individuals with partial response to therapy, complete PV recanalization was achieved in 86% with the continuation of enoxaparin for an extra 6 months. Globally, complete PV recanalization in this study was achieved in 75% of the individuals after a median of 6.5 months.

## 3. Selection of Individuals for Anticoagulation Therapy

Even if anticoagulation therapy is associated with good rates of PV recanalization, the indications for treating PVT in cirrhotic individuals are not well defined in the current guidelines and consensus publications [4, 14]. In fact, the impact of PVT on the evolution of cirrhosis is still a matter of great debate [11] and the clinical benefits of PV recanalization have been demonstrated in only few particular situations.

To date, there is accumulating evidence that cirrhotic individuals with PVT on the waiting list for liver transplantation should be treated with anticoagulation therapy. Indeed, Francoz et al. have demonstrated that complete or partial PV recanalization was associated with a better 2-year survival rate after liver transplantation (82–83% in individuals with partial and complete PV recanalization and 50% in individuals with complete PVT) [7]. This observation is supported by 2 other studies [16, 17]. One study showed a 32% increase in mortality in individuals undergoing liver transplantation with PVT [16]. The other study showed that

the negative impact of PVT on posttransplantation survival was restricted to individuals with an MELD score <15 at the time of surgery [17]. The increased mortality and morbidity associated with PVT are mostly restricted to the first year after liver transplantation [7, 11]. It has also been shown that individuals with PVT at the time of liver transplantation are at higher risk of recurrent PVT after transplant and of requiring retransplantation [8].

Two other situations seem to be logical indications for anticoagulation in cirrhotic individuals with PVT. In acute PVT with extension to the superior mesenteric vein, despite the absence of data, the benefits of anticoagulation seem to exceed the potential risks of intestinal infarction [4, 14]. It also seems reasonable to consider anticoagulation therapy for PVT in cirrhotic individuals with a well-characterized prothrombotic disorder (i.e., the presence of a JAK-2 mutation). In all the other situations, the benefits of anticoagulation are largely unknown.

#### 4. Anticoagulation Regimens for PVT in Cirrhotic Individuals

The optimal anticoagulation regimen for the treatment of PVT has not been determined yet and no clear recommendations exist regarding this question in recent guidelines and consensus publications [4, 14]. The choice of anticoagulation regimen is particularly difficult in the cirrhotic individual, mostly because anticoagulation monitoring is complex in this particular situation.

VKA have been used in some studies to treat PVT in cirrhotic individuals. The rates of complete PV recanalization in cirrhotic individuals treated with VKA are between 42% and 45% [1, 7]. In the study conducted by Francoz et al. in 29 individuals on the waiting list for liver transplantation, complete PV recanalization was achieved in 42% of cases after a mean of 8.1 months of anticoagulation therapy [7]. Of interest, the mean INR before the initiation of treatment was 1.7. In the largest study published on the subject, Delgado et al. treated 29 of the 55 included individuals (53%) with VKA [1]. Complete PV recanalization was achieved in 45% and partial recanalization in 15%. The mean and median INR before VKA therapy was 1.3 (1.1–1.57). In these 2 studies, the target INR was between 2 and 3, with attempt to get as close as possible to 2.5.

The most problematic issue with the use of VKA in cirrhotic individuals is the INR monitoring under therapy. The problem arises from the fact that conventional INR seems to be unreliable in this particular situation [8]. INR has only been validated in individuals with normal liver function on stable anticoagulation [18]. A 29% variation in mean INR has been reported in cirrhotic individuals in a study when three different thromboplastin reagents were used [19]. It is also unclear if a target INR between 2 and 3 is adequate in individuals with abnormal INR values before anticoagulation therapy [3, 8, 11]. Some authors have also raised the potential risk of further lowering protein C levels with the use of VKA: this could theoretically increase the prothrombotic imbalance of individuals with cirrhosis [3, 8].

LMWH has also been used to treat PVT in cirrhotic individuals. In their study, Amitrano et al. included 28 individuals with PVT [11] who were all treated with enoxaparin: complete PV recanalization was achieved in 33% of cases after 6 months of treatment and in 75% of the cases when LMWH therapy was extended an extra 6 months (6–17 months, median 6.5 months). A second study of 38 individuals treated with LMWH reported complete PV recanalization of 50% at 6 months [24]. In a third study, Senzolo et al. reported a 36% complete recanalization rate with nadroparin after a mean of 5.5 months (1–10 months) [6]. LMWH has also been shown to lead to similar rates of portal vein recanalization in individuals with PVT but without cirrhosis [11].

Despite these favorable observations, LMWH therapy is not without any risk either. In the literature, there is little information on the pharmacodynamic profile of LMWH in cirrhotic individuals [20]. Another important issue is that LMWH dosage is based on weight [21]. Cirrhotic individuals often have an increased volume of distribution because of ascites and edema which makes it difficult to determine the optimal dose of LMWH [21]. Recent articles also point to the fact that monitoring of anti-X<sub>a</sub> cannot be used to guide therapy in cirrhotic individuals [8, 20, 21]. Anti-X<sub>a</sub> activity is not a direct measurement of the functional anticoagulant effect of LMWH, but it is instead a surrogate for LMWH concentration in the blood. This measurement is dependent on antithrombin-III (AT) levels, which are decreased in cirrhotic patients [21]. The lower levels of AT found in cirrhosis cause a falsely decreased anti-X<sub>a</sub> activity. Therefore, in the particular case of cirrhosis, anti-X<sub>a</sub> activity is not reliable to evaluate the anticoagulatory effect of LMWH and should not be used to guide anticoagulation therapy because it could be associated with an increased risk of bleeding [21]. Finally, renal function is often altered in cirrhotic individuals (particularly those awaiting liver transplantation): it is well recognized that LMWH is eliminated by the kidneys and that their half-life is increased in that context.

To avoid all the aforementioned problems, an interesting solution could be the use of direct thrombin inhibitors [3]. The potential advantage of these new drugs is that their mechanism of action is independent of AT. However, to date, trials studying direct thrombin inhibitors have specifically excluded cirrhotic individuals.

The choice of the anticoagulation regimen also needs to take into account the potential need to reverse the effect of anticoagulation: this can become necessary in cases of acute bleeding and in all cases undergoing surgery. Whereas the effect of VKA can be quickly and effectively reverted though prothrombin complex concentrate, there is yet no potent and rapidly acting antidote to the effect of LMWH or thrombin inhibitors.

#### 5. Duration of Anticoagulation

The ideal length of anticoagulation therapy for PVT in cirrhotic individuals is not known. However, in the above mentioned studies, a trend for better recanalization rates

seems to stand out with early initiation of therapy. In the study published by Delgano et al., the initiation of anticoagulation <14 days after the diagnosis of PVT was the only predictive factor for complete PV recanalization [1]. In the recently published study of Senzolo et al., early anticoagulation (<6 months after diagnosis) was associated with an odds ratio of 3.3 (CI 1.2–9.4,  $P = 0.004$ ) for complete PV recanalization [6]. In this same study, no PV recanalization was observed if anticoagulation therapy was initiated more than 10 months following the diagnosis of PVT. Consequently, these studies strongly argue in favor of early initiation of anticoagulation therapy. One has however to concede that the diagnosis of PVT is often made fortuitously thus making it difficult to determine when the thrombus started to develop.

No consensus exists also in the optimal duration of anticoagulation therapy in that setting. As shown in the study published by Amitrano et al., individuals with partial response to anticoagulation at 6 months of therapy might benefit from prolonged therapy up to 12 months [11]. In individuals with partial PV recanalization after 6 months, complete recanalization could be achieved in 86% of the cases after a median time of 11 months when anticoagulation was continued, (7–17 months) [11]. In the study conducted by Senzolo et al., it was also shown that continuation of anticoagulation after 12 months in nonresponders was associated with a decreased risk of thrombosis progression (5/12 versus 15/21,  $P < 0.001$ ) [6]. Finally, the study published by Delgano et al. showed high rates of PVT recurrence after discontinuation of anticoagulation [1]. In this study, 38.5% (5/13) of the individuals with complete PV recanalization during the study period stopped anticoagulation and developed recurrent PVT after a median time of 1.3 months following discontinuation of therapy. These studies all suggest that prolongation of therapy should be considered, especially in situations where PV patency is important, namely, in candidates for liver transplantation.

## 6. Complications of Anticoagulation

In noncirrhotic individuals undergoing anticoagulation for PVT, this therapy is considered safe [11, 22, 23]. Indeed, Condat et al. have shown that anticoagulation did not increase the risk (RR 0.9;  $P = 0.9$ ) or the severity of bleeding given that individuals received adequate prophylaxis for gastrointestinal bleeding [22]. However, anticoagulation is more complex in the setting of cirrhosis mostly because of the inherent risk of bleeding secondary to portal hypertension, which can be life threatening [2, 20]. However, it is generally accepted that gastrointestinal bleeding associated with portal hypertension is highly dependent on portal pressure. Any underlying coagulopathy, be it secondary to the liver disease itself or to anticoagulation therapy, should not precipitate bleeding, but could certainly make the bleeding more severe [20]. Therefore, bleeding complications in individuals with cirrhosis undergoing anticoagulation therapy for PVT should not be more frequent.

In published studies, the incidence of bleeding complications has been <5%. In the study published by Francoz et al. where 19 individuals were treated with VKA for a mean time of 8.1 months, only one individual developed a bleeding episode due to postendoscopic variceal ligation ulcer in the esophagus [7]. This individual was successfully treated with proton pump inhibitor and received two packed red blood cells. However, in this study, no information was given on the severity of portal hypertension and if prophylaxis against gastrointestinal bleeding was administered or not. In the study by Amitrano et al., where 28 individuals received enoxaparin, two cases of anemia (hemoglobin drop of 1.5 and 2.0 g/dl, resp.) apparently caused by severe portal hypertensive gastropathy have been described [11]. No case of variceal bleed occurred. In this study, all individuals had screening for esophageal varices and prophylaxis was given to all individuals with varices. In the study published by Delgado et al., during the 19-month study period, 6 variceal bleed occurred but were considered as probably not related to the anticoagulation therapy [1]. However, 5 further bleeding episodes considered secondary to anticoagulation occurred: 1 lower gastrointestinal bleeding, 1 obscure gastrointestinal bleeding, 1 vaginal bleeding, 1 bleeding after dental extraction, and 1 surgical wound hemorrhage. A platelet count  $<50 \times 10^9/l$  was the only factor more frequently associated with bleeding. The use of VKA showed a trend toward increased risk of bleeding but did not reach statistical significance. In the most recently published study, Senzolo et al. showed that bleeding complications secondary to portal hypertension were, in fact, more frequent in cirrhotic individuals with PVT not administered anticoagulation therapy [6]. In that control group, 5 episodes of variceal bleed occurred whereas only one case occurred in the treated group ( $P = 0.09$ ). One individual in the untreated arm died due to a variceal bleed. None of these bleeding complications were secondary to a postligation ulceration in the esophagus. However, in the group receiving anticoagulation therapy, 3 bleeding complications occurred that were not related to portal hypertension (1 epistaxis, 1 hematuria, and 1 cerebral hemorrhage). The individual with intra-cranial bleeding remained with permanent neurologic deficits and this individual had no other risk factor for severe bleeding (platelets count at  $110 \times 10^9$ , normal INR and normal creatinine). In a different type of study published in 2008, cirrhotic individuals receiving anticoagulation therapy for deep vein thrombosis presented bleeding complications in 35% of the cases [24, 25]. In this study, the severity of portal hypertension was not addressed and the risk of bleeding risk was higher in individuals receiving VKA.

## 7. Variceal Bleed Prophylaxis

In the previously described studies, the rate of variceal bleed was low given that individuals had prophylaxis for gastrointestinal bleeding. Therefore, if anticoagulation for PVT in a cirrhotic individual is to be performed, it is preferable to screen for varices before starting anticoagulation. However, in this particular situation, there is no current

consensus or guidelines on whether nonselective beta-blockers, endoscopic variceal ligation (EVL), or combination therapy is better for variceal bleed prophylaxis [2, 4, 13, 14]. In the study published by Senzolo et al., all individuals underwent endoscopic screening for varices at inclusion [6]. Individuals with previous variceal bleed, grade II esophageal varices with red signs or grade III varices were treated by EVL before anticoagulation. The mean number of EVL procedures required to achieve eradication of varices was 2 (1–3 sessions). Anticoagulation therapy was started 15 days after the last EVL. In this study, the authors give no information on the use of beta-blockers. No bleeding secondary to post-EVL ulceration and only one case of variceal bleed occurred under anticoagulation therapy. In Amitrano's study, the strategy used for the prevention of variceal bleeding was different [11]. In the 14/28 individuals presenting with variceal bleed at the time of PVT diagnosis, endoscopic EVL was performed until eradication before starting anticoagulation. The median time from diagnosis to the eradication of varices was 4 months. These individuals also received nonselective beta-blockers before and during anticoagulation therapy. The 14 individuals not presenting with variceal bleed underwent variceal screening and received nonselective beta-blockers if medium-large varices were discovered (no variceal banding). In this study, no case of variceal bleed or post-EVL ulceration was reported. In the Delgado's study, anticoagulation therapy was started after appropriate primary or secondary prophylaxis for variceal bleed. No specific information was given regarding the type of prophylaxis, but 78% of individuals were on nonselective beta-blockers at time zero.

There is a small but definitive and uncontrollable risk of hemorrhage secondary to post-EVL ulceration. Because of this fear, in most studies, the beginning of anticoagulation for PVT has been delayed until complete eradication of varices. However, this delay, as already discussed, could be associated with a lower rate of PV recanalization [1, 6]. One study conducted by Jasmohan et al. in 2008 has looked at the risks of performing EVL at the same time as anticoagulation [26]. A cohort of 5 individuals with esophageal varices (4 with cirrhosis) underwent EVL while on anticoagulation therapy. All individuals had grade 3 or more varices and had therapeutic INR (mean INR 2.3) when ligations were performed. All individuals received nonselective beta-blockers. The mean number of EVL procedures was 3.2/individuals (1–5 sessions). No bleeding complication was reported during the two weeks following each EVL. This small observational cohort needs to be put in the context that post-EVL hemorrhage is thought to occur at a rate of 3–15% [27–29].

Therefore, at this time, no definitive recommendation can be made regarding the optimal prophylaxis against variceal bleed in cirrhotic individuals undergoing anticoagulation for PVT. One needs to determine the importance of starting early anticoagulation in order to achieve rapid portal vein recanalization in each individual versus the risk of bleeding associated with this approach. A careful strategy could be to use nonselective beta-blockers instead of endoscopic variceal ligation if medium-large varices that

have not bled are discovered during screening. More studies are needed before recommendation can be made in favor of EVL under anticoagulation.

## 8. Conclusions and Future Directions

PVT is a common problem in cirrhosis, mostly in individuals with advanced liver disease. PVT is an important prognostic factor of cirrhosis and also bears significance in individuals undergoing liver transplantation. Anticoagulation therapy for PVT in cirrhotic individuals is associated with complete recanalization rates between 33% and 45% after 6 months. Prolonged anticoagulation could be associated with higher complete recanalization rates, lower rates of thrombosis extension, and lower rates of thrombosis recurrence after discontinuation of anticoagulation. To date, no recommendation can be made on whether VKA or LMWH should be preferably used in cirrhotic individuals with PVT. However, it would probably be safer to use LMWH in cirrhotic individuals with abnormal INR before the initiation of anticoagulation therapy. Of note, anti- $X_a$  activity in cirrhosis should not be used to guide therapy with LMWH because of the reduced levels of AT. Bleeding complications secondary to portal hypertension in cirrhotic individuals undergoing anticoagulation for PVT seem to be low but prophylaxis for variceal bleeding probably needs to be administered to all patients. To date, no recommendation can be made on whether EVL, nonselective beta-blockers or combination therapy is better for prophylaxis. In this context, it seems relatively safe to refer to the AASLD guidelines for the management of esophageal varices in this particular situation.

Finally, we cannot make any recommendation regarding the management of PVT in the setting of hepatocellular carcinoma (HCC). This condition needs to be looked for when one makes the diagnosis of PVT in a cirrhotic patient. It bears a different clinical significance and probably is determined by different pathogenic factors. Further studies are needed to determine the optimal management of this condition.

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## Review Article

# Pathophysiology of Portal Hypertension and Esophageal Varices

**Hitoshi Maruyama and Osamu Yokosuka**

*Department of Medicine and Clinical Oncology, Chiba University, Graduate School of Medicine, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan*

Correspondence should be addressed to Hitoshi Maruyama, maru-cib@umin.ac.jp

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Esophageal varices are the major complication of portal hypertension. It is detected in about 50% of cirrhosis patients, and approximately 5–15% of cirrhosis patients show newly formed varices or worsening of varices each year. The major therapeutic strategy of esophageal varices consists of primary prevention, treatment for bleeding varices, and secondary prevention, which are provided by pharmacological, endoscopic, interventional and surgical treatments. Optimal management of esophageal varices requires a clear understanding of the pathophysiology and natural history. In this paper, we outline the current knowledge and future prospect in the pathophysiology of esophageal varices and portal hypertension.

## 1. Introduction

Esophageal varices are the major complication of portal hypertension. It is detected in about 50% of cirrhosis patients, and approximately 5–15% of cirrhosis patients show newly formed varices or worsening of varices each year [1–5]. It is a hemodynamic abnormality characterized by sudden bleeding episode; about a third of all patients with esophageal varices show bleeding episode [6].

A key objective in managing the cirrhotic patients having varices is the primary prevention of bleeding. Either nonselective  $\beta$ -blockers or endoscopic variceal ligation is the treatments of choice for the primary prevention of variceal bleeding [7]. Patients who survive an episode of variceal bleeding are at high risk for rebleeding. Combination of  $\beta$ -blockers and band ligation is the preferred therapy to reduce rebleeding rate [7]. Failures of medical treatment should be managed aggressively with transjugular intrahepatic portosystemic shunting (TIPS), preferably using expanded polytetrafluoroethylene (ePTFE) covered stents [7]. Because of higher rates of morbidity and mortality, rescue derivative surgery should only be considered in low-risk patients.

Optimal management of esophageal varices requires a clear understanding of the pathophysiology and natural history. In this paper, we outline the current knowledge and

future prospect in the pathophysiology of esophageal varices and portal hypertension.

## 2. Pathophysiology of Portal Hypertension and Esophageal Varices

Portal hypertension is associated with both increased portal inflow and increased outflow resistance [8]. Although direct measurement of portal pressure may provide accurate condition, an invasiveness of portal venous catheterization limits the clinical application. Hepatic venous catheterization is the most common technique to determine the portal pressure. Wedged hepatic venous pressure (WHVP) reflects sinusoidal pressures, and hepatic venous pressure gradient (HVPG) is the difference between WHVP and free hepatic venous pressure, being a good predictor for the severity of portal hypertension. Portal hypertension results in the development of collateral vessels, which are the route blood returning to the systemic circulation from portal system bypassing the liver.

## 3. Natural History and Bleeding Risks of Esophageal Varices

Varices may not develop and bleed when the HVPG is lower than 12 mmHg [5, 9]. That is, varices are closely associated

with the condition of HVPG higher than 12 mmHg. Red sign and variceal size (medium to large grade) on endoscopy are representative for bleeding risk of esophageal varices [7, 10]. Severity of liver function reserve and presence of ascites are also important risk factors for variceal bleeding [10].

The bleeding risk decreases over time from the time that varices are identified; most bleeding episodes occur within the first 2 years after identification of varices [6]. Once bleeding occurs, spontaneous cessation of bleeding occurs in only up to 40% of individuals, and the bleeding is associated with the mortality of 20% or more at 6 weeks [11, 12].

Patients who survived an episode of acute variceal hemorrhage have a high risk of rebleeding and death [13]. The median rebleeding rate in untreated individuals is around 60% within 1-2 years of the index bleeding, with a mortality of 33% [14, 15]. Therefore, care should be taken to prevent recurrent bleeding prior to discharge from the hospital for patients who have recovered from an episode of variceal bleeding.

Patients with an HVPG > 20 mmHg measured within 24 hours of variceal bleeding have been identified as being at a higher risk for early rebleeding or failure to control bleeding (83% versus 29%) and a higher 1-year mortality (64% versus 20%) compared to those with lower pressure [16, 17]. Large varices, age over 60 years' old, renal failure, and severe initial bleeding as defined by a hemoglobin <8 g/dL at admission, are the risk factors for early rebleeding [6].

## 4. Pathophysiology of Portal Hypertension and Esophageal Varices

### 4.1. Hepatic Vasodilators

(1) *Nitric Oxide*. Nitric oxide (NO) is a powerful endogenous vasodilator (Table 1), and it modulates the intrahepatic vascular tone [18]. NO is produced from the amino acid L-arginine by NO synthases. It is the natural ligand for soluble guanylate cyclase and is responsible for an increase in the levels of cyclic guanosine monophosphate, the final agent responsible for the relaxation of the vascular wall through the extrusion of cytosolic Ca<sup>2+</sup>.

NO inhibition increases portal pressure in isolated perfused rat livers, and the hepatic response to norepinephrine is markedly enhanced after NO inhibition, suggesting a role of NO in modulating hepatic vascular tone in normal conditions [18]. However, in the cirrhotic liver, the synthesis of NO is insufficient to compensate for the activation of vasoconstrictor systems frequently associated with cirrhosis. This occurs despite a normal expression of eNOS (endothelial NO synthase) mRNA and normal levels of eNOS protein [19], and the decreased activity of hepatic eNOS in cirrhosis is due in part to increased expression of caveolin [20]; as Akt-induced phosphorylation of eNOS reverses inhibitory conformation of eNOS in association with caveolin-1 [21].

The insufficient hepatic NO production may account for the increased intrahepatic vascular resistance in cirrhosis, thereby worsening portal hypertension. These findings may be supported by the data; the infusion of L-arginine, the

TABLE 1: Vasoactive mediators.

Vasodilators	Vasoconstrictors
Nitric oxide	Endothelin
Carbon monoxide	Angiotensin II
Glucagon	Norepinephrine
Endocannabinoid	Vasopressin
Prostaglandin	

precursor of NO biosynthesis, and the administration of nitrates (exogenous donors of NO) decrease portal pressure. Further, enhancement of the expression of NO synthase in liver cells, through the portal injection of adenovirus coupled with the gene encoding NO synthase, significantly reduces portal pressure.

Recent study has shown that myr-Akt gene therapy restored Akt activation and NO production in the cirrhotic liver, suggesting the potential availability of alternative treatment for portal hypertension [22]. The other study reported that simvastatin stimulated hepatosplanchnic output of NO products and decreases hepatic resistance in cirrhosis due to the increased Akt-dependent endothelial NO synthase phosphorylation [23]. The data was supported clinically by the randomized controlled trial [24]. NO also promotes apoptosis of hepatic stellate cell through a signaling mechanism that involves mitochondria, is mediated by reactive oxygen species, and occurs independent of caspase activation [25]. This NO-dependent apoptosis, which may maintain sinusoidal homeostasis, is expected as a future treatment of portal hypertension.

(2) *Carbon Monoxide*. Carbon monoxide (CO), a by-product of heme group oxidation by heme oxygenases (HOs), is considered as an important modulator of intrahepatic vascular resistance [26]. CO activates guanylate cyclase and thereby promotes smooth muscle relaxation, in spite of being less potent than NO. The inhibition of CO production increases portal resistance in normal livers, and HO/CO system is activated in patients with liver cirrhosis. In addition, plasma CO levels directly correlated with cardiac output and inversely with systemic vascular resistance and mean arterial pressure. Thus, CO may be closely related to the hyperdynamic circulatory state in cirrhosis [27].

4.2. *Splanchnic Vasodilatation*. Portal venous inflow tends to increase in cirrhosis, particularly in advanced stages of portal hypertension, due to the vasodilatation in the splanchnic organ. This increased blood flow is one of the key factors which contribute to the pathophysiology of portal hypertension [28]. There are some possible mechanisms which account for the portal hemodynamic abnormalities, neurogenic, humoral, and local mechanisms; vasodilators in the systemic circulation have been examined to explain the pathophysiology of portal hypertension. Increased levels of vasodilators are observed because of impaired hepatic function or development of portosystemic collaterals, as most of them underwent hepatic metabolisms.

(1) *NO*. NO is involved in the regulation of splanchnic and systemic hemodynamics in portal hypertension. Excessive production of NO may be one of major reasons for the vasodilatation, as splanchnic vasoconstrictive effect caused by NO inhibitors in animal is significantly greater in portal hypertension model than control model [29]. An overproduction of NO has also been clearly demonstrated in vitro in perfused mesenteric artery preparations from portal hypertensive rats [18]. Furthermore, the fact that cirrhotic patients show increased levels of serum and urinary concentrations of nitrite and nitrate, which are products of NO oxidation, also supports a role of NO in the pathophysiology of portal hypertension [30]. An increased expression and an increased activity of eNOS account for the increased production of NO. Further, there are some factors which may activate the constitutive NO synthase: shear stress, circulating vasoactive factors (e.g., endothelin, angiotensin II, vasopressin, and norepinephrine), and over-expression of the angiogenic factor vascular endothelial cell growth factor (VEGF) [31]. Recent study suggests that mild increases of portal pressure upregulate eNOS at the intestinal microcirculation through VEGF upregulation [32].

(2) *Glucagon*. Glucagon is a humoral vasodilator which is associated with splanchnic hyperemia and portal hypertension. Two mechanisms are considered for vasodilation by glucagon; relaxing the vascular smooth muscle and decreasing its sensitivity to endogenous vasoconstrictors, such as norepinephrine, angiotensin II, and vasopressin [33]. Plasma glucagon levels are increased in cirrhotic patients and experimental models of portal hypertension, due to decreased hepatic clearance of glucagon as well as an increased secretion of glucagon by pancreatic  $\alpha$  cells [34].

Administration of glucagon antibodies or somatostatin reverses the increase in splanchnic blood flow as a result of normalizing circulating glucagon levels. Additionally, concomitant infusion of glucagon blocks the response in portal hypertensive rat model, and increased circulating glucagon levels in normal rats to values similar to those observed in portal hypertension cause a significant increase in splanchnic blood flow [35, 36]. According to these data, hyperglucagonemia may be responsible for some part of the splanchnic vasodilatation of chronic portal hypertension. The role of glucagon in the splanchnic hyperemia of portal hypertension provides a rationale for the use of somatostatin and its synthetic analogs to reduce glucagon level, thereby treating portal hypertension [37].

(3) *Other Mediators*. CO is one of the vasodilators; an expression and activity of HO are increased in splanchnic tissues in portal hypertension [27]. HO also stimulates VEGF production, resulting in the development of hyperdynamic splanchnic circulation [38].

Recent study has shown that endocannabinoids have a significant role in the hyperdynamic circulation of portal hypertension [39]. Endogenous cannabinoid anandamide is increased in the monocyte fraction of blood from cirrhotic humans and rats, and also expression of the cannabinoid 1

(CB1) receptors is increased in hepatic human endothelial cells. It is considered that activation of endothelial CB1 receptors may stimulate NO production, though the mechanism is unclear. Therefore, inhibition of CB1 receptor blockade may have a possibility of treatment for portal hypertension as a result of reduction of portal flow.

Prostacyclin is an endogenous vasodilator produced by vascular endothelial cells [40]. It causes vascular smooth muscle relaxation by activating adenylate cyclase and augmenting the intracellular level of cyclic adenosine monophosphate. Two different isoforms of cyclooxygenase COX are involved in the biosynthesis of prostacyclin, COX1 and COX2. Both are involved in the increased prostacyclin production by the mesenteric vascular bed of portal vein-ligated rats and the selective inhibition of COX-2 and, to a lesser extent of COX-1, improve the endothelial-dependent vasodilatation in response to acetylcholine [41]. A partial reversal effect for splanchnic vasodilatation after COX blockade might be applicable to ameliorate the hyperdynamic circulation state and/or portal pressure in cirrhosis.

4.3. *Hyperdynamic Circulation*. The portal hypertension is directly related to portal inflow and/or outflow resistance, as determined by Ohm's law "portal pressure = portal venous inflow  $\times$  outflow resistance." Portal venous inflow is affected by hyperdynamic circulation, which is characterized by systemic and splanchnic vasodilatation, low systemic resistance, plasma volume expansion, and high cardiac index [8]. Splanchnic vasodilatation contributes to increasing substantial blood volume which returns to portal venous system. Peripheral vasodilatation activates endogenous neurohumoral systems that cause sodium retention, which leads to expansion of the plasma volume, followed by an increase in the cardiac index. Expansion of plasma volume is a necessary step to maintain an increased cardiac index, which in turn aggravates portal hypertension. This provides the rationale for using a low-sodium diet and diuretics in the treatment of portal hypertension.

4.4. *Portosystemic Collateral Circulation*. The development of portal-collateral circulation is one of the hemodynamic features of portal hypertension. Formation of collaterals is a complex process involving the opening, dilatation, and hypertrophy of preexisting vascular channels. Collaterals develop according to the increased portal pressure, and minimum threshold level of HVPG may be 10 mmHg for the development of portosystemic collaterals and esophageal varices [5, 9].

The vascular resistance of collateral vessels may be a major component of the overall resistance to portal blood flow and, therefore, may be important in determining portal pressure. In addition, although it was traditionally thought that the hyperdynamic splanchnic circulation state associated with portal hypertension was the consequence of active splanchnic vasodilatation, recent data suggests that the increased neovascularization in splanchnic organs plays an important role in allowing the increase in splanchnic

blood inflow [42]. In addition to the increased portal pressure, formation of portosystemic collateral vessels in portal hypertension is influenced by a VEGF-dependent angiogenic process and can be markedly attenuated by interfering with the VEGF/VEGF receptor-2 signaling pathway. This finding suggests that manipulation of the VEGF may be of therapeutic value.

Although the factors which modulate the resistance of collateral vessels have not been clarified, NO may be one of the factors which regulate portal collateral vascular resistance [43]. Effects of isosorbide-5-mononitrate (IMN) and nitroglycerin (NTG) to reduce collateral resistance in cirrhosis may be associated with this NO function. These vessels are also probably hypersensitive to serotonin (5-HT), which markedly increases their vascular tone. In portal hypertensive animals, the administration of selective 5-HT<sub>2</sub> receptor blockers decreases portal pressure.

**4.5. Vasoconstrictors and Hepatic Vascular Bed.** Endothelins (ETs) are a family of homologous 21 amino acid peptides which include ET-1, -2, -3, and -4. They exert various biological effects, vasoconstriction, and stimulation of cell proliferation in tissue. One of the major roles of ET is modulation of vascular tone in cirrhosis [44]. Two major receptors function to mediate, ET-A receptor and ET-B receptor. The former shows a high affinity for ET-1, not for ET-3, and mediates constriction, and the latter has equal affinity for ET-1 and ET-3. Activation of ET-B receptors located on the vascular smooth muscle cells promotes vasoconstriction, whereas activation of ET-B receptors located on endothelial cells promotes vasodilatation, which is mediated by enhanced NO and prostacyclin production by the endothelial cell.

Plasma levels of ET-1 and ET-3 are increased in cirrhotic patients [45]. The level is dominant in patients with ascites. A net release of ET-1 and ET-3 in the splanchnic circulation has been observed in cirrhotic patients but not in controls, suggesting an increased production of ET-1 and ET-3. In fact, increased expression of ET-1 is reported in human cirrhotic livers [46]; endothelial cells, hepatic stellate cells (in their activated phenotype), and bile duct epithelial cells are the major intrahepatic sources of ET-1. However, the precise mechanism and role of ETs in increasing the vascular tone in cirrhosis remains unclear.

Angiotensin II is a powerful vasoconstrictor, which may contribute to increasing hepatic resistance [47]. A-II antagonists, inhibitors of the converting enzyme, or A-II receptors blockers may have a potential to reduce portal pressure, though their effects may be accompanied with systemic hypotension.

Norepinephrine is also a vasoconstrictor, which is involved in the regulation of hepatic vascular tone [48, 49]. The administration of  $\alpha$ -adrenergic antagonists, such as prazosin, inhibits the increase of resistance by norepinephrine. In addition, the hepatic vascular bed of cirrhotic livers exhibits an exaggerated response to the  $\alpha$ -adrenergic agonist methoxamine. This hyperresponse is associated with the

overproduction of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) by COX-1 isoenzyme and is completely corrected by pretreating the livers with nonselective COX blockers, COX-1-selective blockers, or TXA<sub>2</sub> antagonists. Therefore, an increased production of TXA<sub>2</sub> markedly enhances the vasoconstrictive response of the cirrhotic hepatic vascular bed to methoxamine. It remains to be solved, however, that whether this effect is also shared by other vasoconstrictors.

**4.6. Endothelial Dysfunction.** The endothelium under normal condition has a function to produce vasodilators in response to increases in blood volume and blood pressure or to produce vasoconstrictors to prevent or attenuate the concomitant increase in pressure. However, abnormality in the endothelium-related vascular reaction occurs in several pathologic conditions, that is, endothelial dysfunction [50]. It is considered as one of the main mechanisms which account for the increased vascular tone observed in several vascular disorders, such as arterial hypertension, diabetes, and atherosclerosis, and have been attributed to a diminished NO bioavailability or to an increased production of endothelial-derived contracting factors, such as prostaglandin H<sub>2</sub> (PGH<sub>2</sub>)/TXA<sub>2</sub>, ET, or anion superoxide [18]. The intrahepatic vascular bed in cirrhosis also exhibits endothelial dysfunction [51]. Indeed, studies performed both in cirrhotic patients and in experimental models have shown that, contrary to what happens in normal livers, the cirrhotic liver cannot accommodate the increased portal blood flow caused by the postprandial hyperemia, which determines an abrupt postprandial increase in portal pressure [52].

Studies have shown that endothelial dysfunction is associated with an abnormal response to the endothelium-dependent vasodilator acetylcholine [51, 53]. This impaired response may be related to an increased production of TXA<sub>2</sub> and completely prevented by selective COX-1 blockers and TXA<sub>2</sub> antagonists. These data suggest that an increased production of a COX-1-derived vasoconstrictor prostanoids, probably TXA<sub>2</sub>, may be responsible for endothelial dysfunction [53].

Recent studies have shown the possibilities of additional treatments; one is tetrahydrobiopterin, an eNOS cofactor, which increases eNOS activity and significantly improves the vasodilator response to acetylcholine in rats with cirrhosis [54]. It may have a potential role for the treatment of portal hypertension by improving the endothelial dysfunction. The other is "statins," which decreases intrahepatic vascular resistance and improve flow-mediated vasodilation of liver vasculature in cirrhotic liver, due to increase of NO production and improvement of hepatic endothelial dysfunction [23, 24].

## 5. Conclusions

Many advances in the management of portal hypertension and variceal bleeding have occurred over the last 20 years. The key factor for variceal rupture is the wall tension

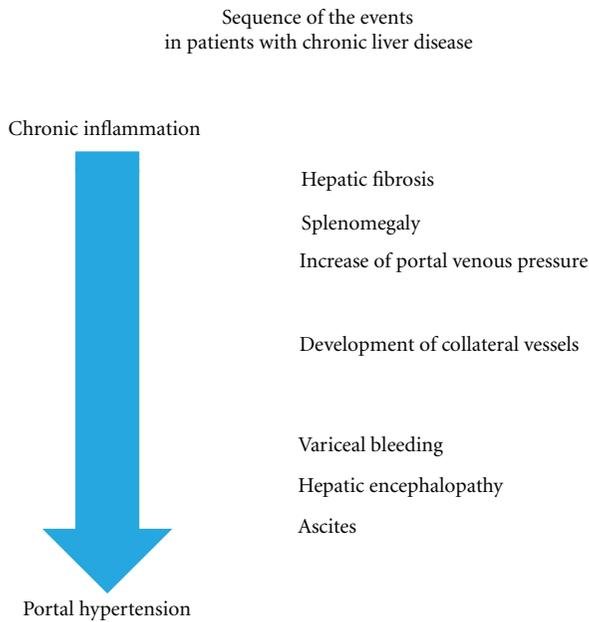


FIGURE 1: Sequence of the events in patients with chronic liver diseases. Possible events are listed from chronic inflammation to portal hypertension.

of varices, which is determined by the “Laplace’s law”: wall tension = (variceal pressure – luminal pressure) × radius/thickening of variceal wall. This tension is the force which is generated by the variceal wall opposing further distension. When the wall tension reaches the critical point of the elastic limit of the varices, rupture occurs. Red sign on endoscopy is a significant indicator to apply prophylactic treatment of esophageal varices. Effective primary prevention for variceal bleeding is now available by nonselective beta blockers or band ligation. Active bleeding should be managed with band ligation alone or combined with somatostatin or octreotide; TIPS and surgery may be positioned as salvage therapy for those who fail endoscopic treatment. Survivors of a variceal bleed should be evaluated for liver transplant.

Since the occurrence of clinical events due to portal hypertension is related to the hemodynamic changes (Figure 1), the goal of long-term pharmacologic therapy in patients with portal hypertension should be a reduction of the HVPg by at least 20% from baseline values and preferably to below the threshold of 12 mmHg. This may explain some of the interindividual variability in hemodynamic response to pharmacological treatment. Recent study has shown that rifaximin may have a possibility to decrease risk of variceal bleeding, and the other complications related to portal hypertension [55]. The pathophysiology in portal hypertension is likely to be multifactorial in origin; various interactive regulations may be present to compensate for the effect of vasoactive mediators. It is a continuous challenge to unveil the mechanism and to develop more effective therapeutic measures.

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## Review Article

# Prevention and Management of Gastroesophageal Varices in Cirrhosis

Yen-I Chen<sup>1,2</sup> and Peter Ghali<sup>1</sup>

<sup>1</sup> Division of Hepatology and Gastroenterology, McGill University Health Center, McGill University, Montreal, QC, Canada H3A 1A1

<sup>2</sup> Internal Medicine Office, Jewish General Hospital, Montreal, QC, Canada H3T 1E2

Correspondence should be addressed to Yen-I Chen, cyen33@gmail.com

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Variceal hemorrhage is one of the major complications of liver cirrhosis associated with significant mortality and morbidity. Its management has evolved over the past decade and has substantially reduced the rate of first and recurrent bleeding while decreasing mortality. In general, treatment of esophageal varices can be divided into three categories: primary prophylaxis (prevention of first episode of bleeding), management of acute bleeding, and secondary prophylaxis (prevention of recurrent hemorrhage). The goal of this paper is to describe the current evidence behind the management of esophageal varices. We will discuss indications for primary prophylaxis and the different modes of therapy, pharmacological and interventional treatment in acute bleeding, and therapeutic options in preventing recurrent bleeding. The indications for TIPS will also be reviewed including its possible benefits in acute variceal hemorrhage.

## 1. Introduction

Portal hypertension in liver cirrhosis results from the anatomical changes and the development of contractile element in the liver vascular bed secondary to progressive hepatic fibrosis and formation of regenerative nodules [1, 2]. The increase in portal pressure triggers splanchnic vasodilation, increased cardiac output, and fluid/salt retention leading to a hyperdynamic circulation and increased portal flow. Formation of collaterals between the portal and systemic systems such as those found in the lower esophagus and gastric cardia (gastroesophageal varices) may not only relieve some of the pressure, but also pose a risk for rupture and bleeding [2].

The prevalence of gastroesophageal varices ranges from 0–40% in compensated cirrhosis to 70–80% in decompensated liver disease, while their growth and progression occur at an estimated 7% per year [2, 3]. The one-year rate of first variceal hemorrhage is 5% for small varices and 15% for large varices [4]. Advanced liver disease (Child B or C), large varices, and varices with red wale marks are bad prognostic signs associated with higher incidence of bleeding. Six-week mortality with each episode of bleeding varies between 15

and 20% and is largely dependent on the severity of the liver disease (0% for Child A and 30% for Child C) [5–7]. Finally, the 1-year rebleeding rate following initial variceal hemorrhage is approximately 60% [8].

The current treatment of gastroesophageal varices has substantially reduced the rate of first and recurrent bleeding while decreasing the mortality of acute variceal hemorrhage [9, 10]. The purpose of this paper is to summarize the management of gastroesophageal varices in terms of primary prophylaxis (prevention of first episode of bleeding), treatment of acute hemorrhage, and secondary prophylaxis (prevention of recurrent bleeding).

## 2. Primary Prophylaxis

Nonselective *beta*-blockers are the current mainstay of therapy in the prevention of first episode variceal hemorrhage [9–11].  $\beta_1$  inhibition reduces cardiac output while  $\beta_2$ -blockade induces splanchnic vasoconstriction and together it results in decreased portal flow and pressure [12]. Nonselective *beta*-blockers used for primary prophylaxis in North America include propranolol and nadolol. Carvedilol has recently

been investigated in portal hypertension given its *alpha*-blocking component and its potential to better diminish portal pressure [13]. However, more data will be needed on its effectiveness and long-term safety. At this time it is premature to endorse Carvedilol as a first-line agent for primary prophylaxis. In terms of dosing and goal of treatment, it is recommended to start at a low dose and to titrate up as tolerated until a heart rate of 55 beats/minute is achieved [9–11].

**2.1. Cirrhosis with Small Varices.** In patients with low-risk small varices (Child A without red wale marks), the use of nonselective *beta*-blocker is optional [9]. There is limited evidence showing that nonselective *beta*-blockers may slow the growth of varices but they do not reduce mortality and their use cannot be universally recommended over regular endoscopic surveillance (every 2 years and annually with hepatic decompensation) [14]. However, nonselective *beta*-blockers are recommended in patients with small varices and high-risk features such as red wale marks and/or Child B-C cirrhosis [9].

**2.2. Cirrhosis with Medium to Large Varices.** A large meta-analysis looking at propranolol/nadolol versus placebo, in patients with cirrhosis and medium to large varices, found a significantly lower incidence of first variceal bleeding in the treatment group: 14% compared to 30% [4]. Also, these nonselective *beta*-blockers may be equivalent to endoscopic variceal band ligation (EVBL) in terms of primary prevention and mortality rate [15, 16]. In addition, they are inexpensive and can potentially prevent other complications of cirrhosis such as spontaneous bacterial peritonitis and bleeding from portal hypertensive gastropathy [17, 18]. However, 15–20% of patients treated with nonselective *beta*-blockers are noncompliant due to common side effects such as fatigue, dizziness, and shortness of breath. EVBL is associated with fewer side effects and does not rely on patient compliance but requires technical expertise and can lead to serious complications such as bleeding from ligation-induced ulcers [12, 19]. Finally, a randomized controlled trial comparing EVBL and propranolol to EVBL alone in patients with large varices did not show a difference in terms of mortality or incidence of first bleed [20]. Therefore, depending on patient/physician preference and available expertise either nonselective *beta*-blocker or EVBL alone should be used for primary prophylaxis in cirrhosis with medium to large varices. Combination therapy does not seem to confer any additional benefit (Table 1).

### 3. Acute Variceal Bleeding

The management of acute variceal bleeding with the combination of vasoconstrictors, endoscopic therapy, and antibiotics has decreased mortality substantially [9, 10]. Initial assessment of a patient with acute variceal hemorrhage begins with the evaluation of airway, breathing, and circulation. Many of these patients are at risk for aspiration and intubation is often performed for airway protection, although there are limited data to justify this practice [21, 22]. Volume

resuscitation with blood and fluid is essential in the initial stabilization; however, experimental studies suggest that overly aggressive volume repletion can worsen bleeding and increase the rate of rebleeding and mortality [23]. Therefore, meticulous resuscitation with a target hemoglobin level of 8 g/dL is recommended [23, 24]. In addition, animal studies suggest that blood transfusion may be superior to fluid administration given that fluid resuscitation may decrease blood viscosity, which can exacerbate portal pressure and potentially worsen acute variceal hemorrhage [25]. Correction of significant coagulopathy and thrombocytopenia with fresh frozen plasma and platelet transfusions should also be considered [10]. Studies on Factor VIIa have failed to show benefit in terms of mortality and control of bleeding and its use is currently not recommended [6].

### 4. Antibiotics in Acute Variceal Bleeding

Acute variceal hemorrhage has been shown to increase the risk for severe bacteremia, which is associated with higher mortality rates and greater incidence of rebleeding [26–28]. Meta-analyses have revealed that antibiotic prophylaxis can improve short-term survival while decreasing bacterial infections and rebleeding rates [26, 29, 30]. Oral norfloxacin or intravenous ciprofloxacin for 7-days, administered at the time of acute bleeding, works by decreasing the amount of gram-negative bacteria in the gut believed to be the most common source for infection in cirrhosis [27, 28]. However, in patients with advanced cirrhosis (Child B/C) ceftriaxone may be superior to norfloxacin in preventing infections [28]. This is likely due to ceftriaxone's extended coverage against nonenterococcal streptococci and quinolone-resistant Gram-negative bacteria. Therefore, cirrhotic patients without advanced liver insufficiency and acute variceal hemorrhage should receive either oral norfloxacin or IV ciprofloxacin for 7 days while ceftriaxone is preferred in patients with Child B/C cirrhosis or previous quinolone use.

### 5. Pharmacological Therapy and Endoscopic Management

In addition to antibiotics, vasoactive agents such as vasopressin, terlipressin, somatostatin, and octreotide play a major role in controlling acute esophageal variceal hemorrhage through their ability to induce splanchnic vasoconstriction thereby reducing portal flow and pressure [9, 10]. In fact, they may be equally as effective as endoscopic sclerotherapy in controlling initial bleeding and in preventing rebleeding with less adverse effects [31, 32]. These agents, when administered at the time when variceal bleeding is suspected, can achieve initial hemostasis in 60–80% of the cases [33].

Vasopressin is a potent vasoconstrictor that reduces blood flow to all splanchnic organs leading to substantial decreases in portal pressure [10]. However, its use has been limited by its side effects such as hypertension, cardiac, and peripheral ischemia, and ischemic bowel. Terlipressin is a synthetic analogue of vasopressin with longer pharmacological activity and fewer side effects [4, 10, 34]. The intact

TABLE 1: Primary prophylaxis and surveillance.

Surveillance/prophylaxis modalities	Indications	Dose	Goal
Endoscopic surveillance	Low-risk* small varices (not on nonselective BB**)	Every 2 years and annually with liver decompensation	Surveillance for progression into higher-risk lesions needing medical or endoscopic prophylaxis
Nadolol	High-risk*** small varices and medium-large varices <i>Optional:</i> low-risk small varices	Start: 40 mg qd	Titrate to heart rate: 55 beats/minute or maximally tolerated dose
Propranolol	High-risk small varices and medium-large varices <i>Optional:</i> low-risk small varices	Start: 10 mg bid	Titrate to heart rate: 55 beats/minute or maximally tolerated dose
EVBL	Medium to large varices	Every 2–4 weeks	Until variceal obliteration

\* Low-risk: Child A cirrhosis and no red wale marks, \*\* *beta*-blocker, \*\*\* high-risk: Child B or C cirrhosis and/or presence of red wale marks.

molecule has immediate vasoconstrictive activity, which is followed by a delayed effect secondary to a slow enzymatic breakdown of terlipressin into vasopressin. It is the only agent that has been demonstrated to decrease mortality in acute variceal hemorrhage [4]; however, it is not yet available in North America. In terms of dosing, terlipressin is given intravenously and should be started at 2 mg every 4 hours for 48 hours, followed by 1 mg every 4 hours [9]. The optimal duration of treatment is unknown but current recommendations suggest a total of 2–5 days.

Somatostatin is a naturally occurring tetradecapeptide that has inhibitory effects on exocrine/endocrine hormones, gastrointestinal motility, and systemic blood flow leading to a decreased circulation and pressure in the portal and portocollateral system [34]. Octreotide, a synthetic analogue of somatostatin with greater potency and longer half-life, is the only substance available in North America mainly due to its safety profile and its apparent effectiveness when used in combination with EVBL [9, 34, 35]. However, its effectiveness in controlling acute variceal hemorrhage has not been firmly established [11, 34]. In terms of dosing, it is administered intravenously and should be initiated with a 50 mcg bolus followed by an infusion at 50 mcg/hr [9]. A bolus can be repeated in the first hour if variceal hemorrhage is uncontrolled. As with terlipressin therapy should be continued for 2–5 days (Table 2).

Following initiation of vasoactive agents, EGD should be performed within 12 hours of presentation [10]. EVBL is superior to sclerotherapy and is the modality of choice [19]. The combination of EVBL with pharmacological therapy is the current standard of care and when compared to EVBL alone it improves initial control of bleeding and 5-day hemostasis without a mortality benefit [36].

## 6. Role of TIPS in Acute Variceal Bleeding

The use of transjugular intrahepatic portosystemic shunt (TIPS) in acute variceal hemorrhage has been historically reserved for salvage therapy in patients who have failed endoscopic and pharmacological treatment. However, a recent randomized controlled trial looking at early TIPS, defined as within 72 hours of standard therapy (EVBL + antibiotic +

vasoactive agent), versus standard therapy alone showed that in patients with Child B/C cirrhosis the early use of TIPS was associated with a reduction in the failure to control bleeding, lower incidence of rebleeding, and decreased mortality rate [37]. In addition, the TIPS group did not have an increased incidence of hepatic encephalopathy. Notably, however, the outcomes in the nonearly TIPS group were unusually poor. Although more studies will be needed to confirm these findings, the early use of TIPS should be considered in patients with severe liver disease who present with acute variceal bleeding following initial standard therapy.

## 7. Secondary Prevention

Patients who survive an episode of acute variceal hemorrhage are at high risk of recurrence. Overall, 60% of these individuals will rebleed within 2 years with a mortality rate of 33% [4, 8]. Therapy aimed at reducing this risk is essential and should be implemented as soon as the initial hemorrhage is controlled [9, 10]. Multiple modes of treatment have been investigated including monotherapy with nonselective *beta*-blockers, combination medical therapy, EVBL with or without pharmacological adjunct, and TIPS.

Nonselective *beta*-blockers have been shown to decrease rebleeding rates from 60% to 42–43% likely secondary to the decrease in portal pressure [4, 8, 24]. Further portal pressure reduction can be achieved when they are combined with oral nitrates (ISMN) [38]. Nitrate-induced venodilation decreases cardiac output and blood pressure, which can lead to a baroreceptor-mediated splanchnic vasoconstriction and fall in portal pressure [39]. It may also have a direct vasodilatory effect on the portosystemic circulation; however, a randomized trial and a recent meta-analysis did not show any benefit in adding a nitrate. In addition, combined therapy is associated with more adverse effects leading to discontinuation of treatment [40, 41].

In terms of endoscopic therapy, EVBL is superior to sclerotherapy and is the method of choice [42, 43]. Meta-analysis of several randomized controlled trials (719 patients) comparing EVBL versus combination medical therapy, with nonselective *beta*-blockers and nitrates, showed no difference in rebleeding rate and increased survival in the medically

TABLE 2: Initial medical management of acute variceal bleeding.

Treatment	Dose	Duration	Details
Antibiotics			
Ceftriaxone	1 g IV daily	5–7 days	Severe cirrhosis Child B/C and/or high suspicion of quinolone resistance
Ciprofloxacin	400 mg IV or 500 mg oral twice daily	5–7 days	Mild cirrhosis Child A and low suspicion of quinolone resistance
Norfloxacin	400 mg oral twice daily	5–7 days	Mild cirrhosis Child A and low suspicion of quinolone resistance
Vasoconstrictors			
Octreotide	50 µg IV bolus, then infusion at 50 µg/hr	2–5 days	Initial bolus can be repeated in the first hour if bleed not controlled
Terlipressin	2 mg IV every 4 hr × 48 hr, then 1 mg IV every 4 hr	2–5 days	Not available in North America
Somatostatin	250 µg IV bolus, then 250–500 µg/hr	2–5 days	Not available in North America

treated group [44–47]. Also, two prospective trials suggest that the combination of EVBL with medical therapy (nadolol) may be superior to EVBL alone [48, 49]. The use of EVBL and a nonselective *beta*-blocker is the current recommendation for secondary prophylaxis and should be instituted without delay following initial bleed [10]. However, a recent randomized controlled trial looking at combination therapy (EVBL + nadolol + nitrate) versus medical therapy alone (nadolol + nitrate) found no difference in rebleeding rates, need for rescue therapy, or mortality while the combination therapy was associated with more adverse events [50]. More studies will be needed to confirm these findings but future guidelines may move towards medical therapy alone.

Finally, TIPS in secondary prophylaxis has been shown to lower rebleeding rates when compared to the aforementioned medical/endoscopic therapy [51–53]. However, no mortality benefit has been demonstrated with TIPS and its use is associated with higher costs and incidence of hepatic encephalopathy. Therefore, the use of TIPS in secondary prophylaxis is not recommended; however, its use may be considered following failure with conventional medical therapy [10]. This may change with the advent of polytetrafluoroethylene- (PTFE-) covered prostheses, which substantially improves TIPS patency.

In summary, EVL in combination with nonselective *beta*-blockers is the method of choice in preventing recurrent variceal bleeding. The addition of nitrates can theoretically potentiate the portal pressure drop; however, it has not been shown to decrease mortality or rebleeding rates and is associated with greater side effects. TIPS is not recommended for secondary prophylaxis and should only be considered following failure with usual medical therapy. It decreases rebleeding rates without a mortality benefit while being associated with higher costs and incidence of hepatic encephalopathy. Whether the new PTFE covered stent will improve TIPS efficacy in secondary prophylaxis remains to be seen, but for the moment its use is restricted to those cases where other therapies have failed.

## 8. Conclusion

The management of gastroesophageal varices has evolved over the last decade resulting in improved mortality and morbidity rates. Primary prevention with nonselective *beta*-blockers or EVBL should be initiated in all patients with medium to large varices and in patients with small varices associated with high risk features such as red wale marks and/or advanced cirrhosis. While prophylaxis in patients with small varices without high risk features is considered optional. In acute bleeding, vasoactive agents such as octreotide or terlipressin should be initiated along with antibiotics followed by EVBL within 12 hours of presentation. These patients are at increase risk for rebleeding and secondary prevention should be initiated immediately following control of initial hemorrhage with serial EVBL and nonselective *beta*-blocker. Currently, TIPS' role in secondary prophylaxis is limited except for failure with conventional therapy; however, this may change with the advent of PTFE covered stents. Although therapy for patients with varices has made significant progress, it will continue to improve with better endoscopic technique, novel pharmacological agents, greater efficiency of liver transplant, and more effective rescue therapy.

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## Review Article

# Towards Noninvasive Detection of Oesophageal Varices

**Kara Rye, Robert Scott, Gerri Mortimore, Adam Lawson, Andrew Austin, and Jan Freeman**

*Liver Unit, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE, UK*

Correspondence should be addressed to Jan Freeman, j.freeman115@btinternet.com

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Current guidelines recommend that all cirrhotic patients should undergo screening endoscopy at diagnosis to identify patients with varices at high risk of bleeding who will benefit from primary prophylaxis. This approach places a heavy burden upon endoscopy units and the repeated testing over time may have a detrimental effect on patient compliance. Noninvasive identification of patients at highest risk for oesophageal varices would limit investigation to those most likely to benefit. Upper GI endoscopy is deemed to be the gold standard against which all other tests are compared, but is not without its limitations. Multiple studies have been performed assessing clinical signs and variables relating to liver function, variables relating to liver fibrosis, and also to portal hypertension and hypersplenism. Whilst some tests are clearly preferable to patients, none appear to be as accurate as upper GI endoscopy in the diagnosis of oesophageal varices. The search for noninvasive tests continues.

## 1. Introduction

Cirrhosis is the end stage of every chronic liver disease, resulting in formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension. Portal hypertension is associated with development of a hyperdynamic circulation and complications such as ascites, hepatic encephalopathy, and oesophago-gastric varices. Patients with cirrhosis and gastro-oesophageal varices have a hepatic venous pressure gradient during haemodynamic catheterization of at least 10–12 mmHg [1]. Oesophageal varices are present at diagnosis in approximately 50% of cirrhotic patients, being more common in Child-Pugh class C patients compared to Child-Pugh class A patients (85% versus 40%) [1, 2]. De novo formation of varices occurs at a rate of 5% per year, with a higher incidence in patients continuing to consume alcohol or with worsening liver function [2]. Once varices form, they enlarge from small to large at a rate of 5–12% per year [2] and bleed at a rate of 5–15% per year. The greatest bleeding risk is seen in large varices classified as being >5 mm diameter and is also influenced by liver disease severity as assessed by Child-Pugh score, and by the presence of red wale markings on varices at endoscopy. Therefore, these factors should also be taken into consideration to classify “high-risk varices” [3].

Reports from the 1940's to the 1980's demonstrate poor outcomes from variceal bleeding with mortality rates between 30–60% [4–6], but studies suggest that the outcomes have improved over the last few decades [7–9]. This is demonstrated in a study by Carbonell et al. [10], who showed that between 1980–2000, the inhospital mortality from variceal bleeding decreased from 42.6% to 14.5% and was associated with decreased rebleeding and rates of bacterial infection.

Although mortality from a bleeding episode has decreased with improved endoscopic and radiological techniques together with new pharmacologic therapies, a 20–30% mortality [11] means that bleeding from oesophageal varices remains of significant clinical importance. Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis clearly show that the risk of variceal haemorrhage can be reduced by 50% to about 15% for large oesophageal varices [12]. Current guidelines, therefore, recommend that all cirrhotic patients should be screened for varices at diagnosis, with followup every 2–3 years for patients without varices (depending upon liver disease severity) and 1–2 years for patients with small varices, to assess for enlargement of varices and need for prophylactic treatment [13]. Upper GI endoscopy remains the gold standard for screening, but this test is not without its own limitations. There is conflicting evidence with regard to the

interobserver agreement for endoscopic diagnosis of variceal presence, grade, or presence of red signs [14–16]. Cales et al. found in 100 cirrhotic patients that the interobserver agreement between four independent observers for the size of oesophageal varices and presence of red signs was good with kappa values of 0.59 and 0.60, respectively. However, Bendtsen et al. found considerable variation in the interobserver agreement on the diagnosis and grading of oesophageal varices between 22 endoscopists with a large variation in kappa values. The current guidelines cause a significant burden and cost to endoscopy units and necessitate patients having repeated unpleasant procedures even when up to 50% may still not have developed oesophageal varices 10 years after the initial diagnosis [2].

If it were possible to predict oesophageal varices by noninvasive means this would restrict testing to the population deemed to be at most risk and reduce the number of endoscopies required. Such a screening test should be simple, quick, reproducible, and cost effective. The utility of current noninvasive tests to predict oesophageal varices will be reviewed in this paper.

## 2. Current Perspectives: Possible Approaches to Noninvasive Diagnosis of Oesophageal Varices

*2.1. Physical Examination and Laboratory Parameters.* Several studies have examined the usefulness of different clinical and laboratory parameters as predictors of the presence or size of oesophageal varices. These are discussed below.

*2.1.1. Physical Signs and Variables Related to Liver Function.* A number of clinical signs and other laboratory markers have been identified either alone or in combination as factors predicting the presence of oesophageal varices. These include the presence of spider naevi, splenomegaly or ascites, Child-Pugh classification, serum albumin, and prothrombin time.

Spider naevi, a low-albumin and low-platelet count were shown to be independent risk factors for the presence of varices in a study by Garcia-Tsao et al. [17]. In a further study by Berzigotti et al. [18], spider naevi, ALT, and albumin were found to predict oesophageal varices with the best cutoff giving a sensitivity of 93%, specificity of 37%, and correctly classifying 72% of patients. Similarly, spider naevi have been found to be predictive of large oesophageal varices with a diagnostic accuracy of 72% when using the variables platelet count, prothrombin index, and spider naevi [19]. Chalasani et al. [20] found that splenomegaly detected on clinical examination was an independent risk factor for the presence of large varices. Zaman et al. [21] demonstrated that cirrhotic patients in Child-Pugh classes B or C were almost 3 times as likely to have oesophageal varices or large oesophageal varices as compared to patients in Child-Pugh class A.

The Baveno IV International Consensus Workshop on methodology of diagnosis and treatment concluded that no study reached a high enough level of significance to

warrant the widespread use of such noninvasive markers of oesophageal varices [13].

*2.1.2. Variables Related to Liver Fibrosis.* Chronic liver injury and inflammation leads to fibrosis and ultimately cirrhosis, through the deposition of extracellular matrix (ECM) complexes. The collagen fibrils of the complex undergo secondary processing, becoming cross-linked, which confers resistance to degradative enzymes and irreversibility [22]. Normally, deposition of the ECM is a dynamic, reversible process with removal of ECM mediated by several specific matrix metalloproteinases (MMPs), which in turn are regulated by soluble inhibitors termed TIMPs (tissue inhibitor of metalloproteinase). A number of serum markers for ECM deposition and removal have been evaluated as candidate markers for liver fibrosis, and a small number of studies have evaluated their usefulness in predicting oesophageal varices. Potential markers examined to date include the glycoproteins, hyaluronic acid and laminin, and members of the collagen family including procollagen III and type IV collagen. Conflicting results have been demonstrated. Galal et al. [23] assessed the ability of serum hyaluronic acid to predict medium-to-large oesophageal varices and showed the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy at a cutoff of 207  $\mu\text{g/L}$  to be 94%, 77.8%, 88.7%, 87.5%, and 88.3%, respectively. Körner et al. [24] showed no association between concentrations of hyaluronic acid or laminin and grade of oesophageal varices, and a further study by Bahr et al. [25] confirmed the lack of association of serum laminin to size of oesophageal varices.

Similar conflict is seen when examining the evidence with regard to the role of the collagens. In the first of only 2 studies in this area, the aminoterminal propeptide of type III procollagen was shown to have a weak correlation to the degree of oesophageal varices [26]. The second study by Mamori et al. [27] included 44 patients with alcoholic liver disease and demonstrated a significant difference in serum type IV collagen levels between patients with and without varices (712.3 versus 404.3 ng/mL,  $P < 0.001$ ), giving an AUROC of 0.78 for predicting the presence of oesophageal varices.

None of the aforementioned markers could currently be utilised to predict oesophageal varices in portal hypertension; in view of this several different biomarkers have been combined with the aim of improving their diagnostic ability. FibroTest is a composite score generated by combining the results of five serum blood tests (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin,  $\gamma$ -glutamyltranspeptidase, and bilirubin and alanine) corrected for the age and gender of the patient. Results have shown high predictive values for significant fibrosis in patients with chronic hepatitis C, chronic hepatitis B, fatty liver disease, and chronic alcoholic liver disease [28–31]. A single study has assessed the predictive value of fibroTest in the diagnosis of large oesophageal varices in 99 cirrhotic patients [32]. Significant differences in FibroTest value (0.89 versus 0.82), platelet count (110 versus 150), and prothrombin time (50 versus 66%) were seen between patients with and without large

oesophageal varices. FibroTest had the highest discriminative power of all the variables with an AUROC curve of 0.77. Using a cutoff of 0.80, this gave a sensitivity of 92%, specificity 21%, PPV 33%, and NPV 86%. A fibroTest score < 0.75 was found to be associated with the absence of large oesophageal varices with a NPV of 100%. The limitations to the study are that it was a retrospective study with significant population bias and has not been reproduced in a prospective study of compensated cirrhotics. FibroTest is not readily available to most clinicians, which limit its utility as a screening test.

*2.1.3. Variables Related to Portal Hypertension and Hypersplenism.* Thrombocytopenia may occur in portal hypertension-induced splenomegaly, in part due to platelet sequestration, and a large number of studies have been performed assessing the relationship between platelet count and oesophageal varices [17, 19–21]. A low-platelet count is regularly identified as predictive of oesophageal varices and large oesophageal varices, but there is a wide variation in the cut-off level of platelets used, ranging from 68,000 to 160,000 with sensitivities ranging from 71–90% and specificities from 36–73%. Bias is likely to account for much of this variation, with the majority of studies being retrospective in nature, having heterogeneous cohorts of patients resulting in both selection and spectrum bias.

A longitudinal study by Qamar et al. [33] of 213 patients, with compensated cirrhosis with portal hypertension but without varices, demonstrated that the median platelet count at the time of occurrence of varices was 91,000. However, no platelet count could be identified that accurately predicted the presence of oesophageal varices (AUROC curve 0.63), and they, therefore, concluded that platelet count is an inadequate noninvasive marker for prediction of the presence of oesophageal varices. In an attempt to improve the predictive value of the platelet count, it has been combined with other variables, and the results of these studies are discussed below.

Oesophageal collaterals develop as a consequence of portal hypertension, being formed by vascular remodelling and angiogenesis. Key molecules thought to be involved in this include nitric oxide and vascular endothelial growth factor (VEGF). A single study of 85 cirrhotic patients examined the predictive capability of serum nitrate levels to detect oesophageal varices [34]. Significant differences in serum nitrate levels were found between patients with large oesophageal varices compared to patients without oesophageal varices ( $P < 0.01$ ). The best cut-off level for prediction of oesophageal varices was  $38 \mu\text{mol/L}$ , giving a sensitivity 86.5%, specificity 83.3%, PPV 95%, and NPV 62.5%. Animal studies suggest that the formation of oesophageal varices results not only from opening up of preexisting collateral vessels but also as a result of angiogenesis which may in part be mediated by VEGF. Use of VEGF as a noninvasive biomarker has only been investigated in a single study, and no correlation between VEGF levels and grade of oesophageal varices was detected [35].

The development of portosystemic collaterals and the resultant shunting is responsible for the complication hepatic encephalopathy, in which ammonia plays a role. One study has examined the role of blood ammonia concentrations in the noninvasive detection of oesophageal varices [36]. In this study of 153 cirrhotic patients, a significant correlation was demonstrated between oesophageal variceal grade and venous ammonia levels ( $r = 0.43$ ,  $P < 0.001$ ). The AUROC curve for predicting the presence of oesophageal varices was 0.78, and using a cut-off of  $42 \mu\text{M/L}$  this gave a sensitivity of 92% and a specificity of 60%.

Therefore, variables associated with portal hypertension and hypersplenism are not accurate enough to be used as noninvasive markers of oesophageal varices.

#### *2.1.4. Predictive Scores*

*(1) Platelet Count/Spleen Diameter Ratio.* This ratio is calculated by dividing the platelet number/ $\text{mm}^3$  by the maximum spleen bipolar diameter in mm as estimated by abdominal ultrasound. There have now been a number of studies assessing this. The first by Giannini et al. in 2003, reported the platelet count/spleen diameter ratio to be the only independent variable associated with presence of OV on multivariate analysis and identified a cut-off value of 909, giving a PPV of 96% and NPV of 100% [37]. The second part of the study confirmed the reproducibility of this cut-off level with a PPV of 74% and NPV of 100% in compensated cirrhotic patients. The same group then followed up 68 patients without OV with repeat endoscopy and calculation of the platelet/spleen diameter ratio. At followup, patients with a platelet count/spleen diameter ratio <909 had 100% NPV and 84% PPV, and they concluded that the platelet count spleen diameter ratio was effective in ruling out the presence of OV when cirrhotic patients were followed longitudinally. Subsequently, a multicentre, international validation study using the 909 ratio was performed in 218 patients [38]. The test performed less well than in the original study with a PPV of 76.6% and a NPV of 87.0%. This has been a consistent feature in all studies subsequently performed which vary from being retrospective or prospective in nature and utilise different cut off points [39–43]. Therefore, despite promising early results the platelet count/spleen diameter ratio is not a reliable tool to screen for oesophageal varices.

*(2) Platelet Count and Child-Pugh Class.* In 2007, Burton et al. published the validation of a model for predicting size and presence of varices based upon platelet count and Child-Pugh class [44]. The first model aimed to detect large varices in Child-Pugh A patients with a platelet count <80 and had a sensitivity of 58%, specificity 79%, PPV 30%, and NPV 92%. The second model aimed to identifying any varices in Child B/C patients with a platelet count <90 and had a sensitivity of 60%, specificity of 59%, PPV 80%, and NPV 34%. Once again, the performance of these models would not reliably predict the presence of oesophageal varices.

(3) *AST/ALT Ratio*. The AST/ALT ratio has been used to predict cirrhosis, and by natural extension studies have been performed to assess its usefulness in predicting oesophageal varices. In a retrospective study [45], significantly higher AST/ALT ratios were seen in patients with varices compared to those without (ratio: 1.8 versus 1.0,  $P < 0.0001$ ). A further prospective study [46] found an AST/ALT ratio  $> 1.12$  to be significantly associated with the presence of varices at initial endoscopy (OR 3.9,  $P = 0.02$  95% CI 1.3–11.8). This cutoff gave a sensitivity of 47.8%, specificity of 87%, PPV 42.3%, and NPV 89.2%, and an AUROC of 0.69. A further study using a different cut-off of  $\geq 1.0$  demonstrated a sensitivity of 68%, specificity of 89%, PPV 77%, and NPV 83%, with an AUROC 0.83 (0.72–0.94) for predicting the presence of oesophageal varices [47]. For the prediction of large oesophageal varices, this gave a sensitivity 68%, specificity 77%, PPV 41%, and NPV 92%, and AUROC 0.79 (0.64–0.94). Overall, the AST/ALT ratio correctly classified 81% patients for the detection of varices and 76% of those with large varices. Therefore these studies, which include patients with different aetiologies of liver disease and used different cutoffs for the AST/ALT ratio cannot confidently predict the presence of oesophageal varices in clinical practice to avoid screening all cirrhotic patients with endoscopy.

(4) *Right Lobe Liver Albumin Ratio*. This ratio is calculated by dividing the right liver lobe diameter (as assessed by abdominal ultrasound and measured in millimetres) by the serum albumin concentration (g/L). This has been assessed in a single study of 94 cirrhotic patients [48]. Right liver lobe/albumin ratio correlated with presence and size of oesophageal varices ( $r = 0.488$ ,  $P < 0.01$ ;  $r = 0.481$ ,  $P < 0.01$ , respectively). For a cut-off value of 4.425 this gave a sensitivity of 83.1% and specificity 73.9% and thus once again cannot be used as a reliable screening test.

## 2.2. Transient Elastography

**2.2.1. Liver Stiffness.** Transient elastography (TE, FibroScan, Echosens, France) is a noninvasive technique developed to assess hepatic fibrosis in patients with chronic liver diseases. Fibrosis causes an increase in liver stiffness, and measurement of this forms the basis of TE, which is painless, rapid, and easy to perform. Studies suggest that TE is highly reproducible and reliable with very high interobserver and intraobserver agreement overall but that patient related and liver disease related factors may have a negative effect on the reproducibility of this technique [49]. A wide range of liver stiffness values have been reported ranging from 2.5 to 75 kPa, being influenced by gender, body mass index, disease aetiology, and presence of necroinflammatory change [50–53]. As a rough guide, normal TE values are considered to be 3.8–8 kPa in men and 3.3–7.8 kPa in women, significant fibrosis (Metavir fibrosis stage  $\geq 2$ ) 7–8 kPa and cirrhosis 13–17 kPa.

A number of studies have been performed examining the relationship of liver stiffness to size and presence of oesophageal varices, and these results are summarised in

Table 1 [47, 54–57]. These studies demonstrate a significant correlation between liver stiffness measurements and the presence of oesophageal varices but are divided with regard to the relationship of liver stiffness to variceal size.

For the diagnosis of variceal presence, AUROC curves varied from 0.76–0.85, with a sensitivities of 84–95%, specificities of 43–78%, PPV 57–89%, and NPV 66–91% using cutoffs between 13.9–21.5 kPa. For the diagnosis of large oesophageal varices, AUROC varied from 0.76–0.87, with sensitivities of 77–91%, specificities of 60–85%, PPV 48–56% and NPV 94–95% using cut-offs between 19–30.5 kPa. The other limitations of the study relate to inclusion of patients with liver disease of different aetiologies and of different severity, according to Child-Pugh class.

The study by Castera et al. best represents the cohort of patients in whom noninvasive screening for varices is needed [47]. All 70 patients were Child-Pugh class A and had cirrhosis secondary to hepatitis C. They demonstrated that LSM values increased with the grade of OV ( $P < 0.001$ ). The AUROC for presence of OV was 0.84 and 0.87 for large OV. A cutoff of 21.5 kPa predicted the presence of OV with a sensitivity of 76%, specificity 78%, PPV 68%, and NPV 84% and correctly classified 73% of patients. At a cutoff of 30.5 kPa, the presence of large OV was predicted with a sensitivity 77%, specificity 85%, PPV 56%, and NPV 94%, and correctly classified 79% of patients.

Therefore, the predictive performance of liver stiffness measurement is poor for the diagnosis of OV with low specificity and PPV, particularly with regard to large OV. However, it may be useful as a screening test to identify patients in whom variceal screening is not required, but at present cannot be advocated as a surrogate for gastroscopy.

**2.2.2. Spleen Stiffness.** Transient elastography has also been used to determine spleen stiffness, using the hypothesis that splenomegaly resulting from portal hypertension causes changes in the spleen's density. In a study of 191 patients (135 cirrhotic) recently published, it was demonstrated that spleen stiffness was significantly higher in cirrhotics than noncirrhotics and in patients with oesophageal varices compared to those without [58]. 52.5 kPa was determined to be the best cutoff giving an AUROC curve of 0.74. They found a better diagnostic accuracy, of 89.95%, in predicting the presence but not the grade of oesophageal varices when liver and spleen stiffness were used together.

MR Elastographic spleen stiffness has also been assessed in a small study of 17 compensated cirrhotics. All of the 7 patients with oesophageal varices had a mean spleen stiffness of  $> 10.5$  kPa [59]. Further larger studies are needed to investigate the diagnostic accuracy of MR Elastographic spleen stiffness for noninvasive prediction of oesophageal varices.

## 2.3. Other Imaging Modalities

**2.3.1. Ultrasound.** Doppler ultrasonography (US) imaging provides a real-time, inexpensive, and repeatable examination of the portal system and allows estimation of both

TABLE 1: Summary of diagnostic accuracy of LSM for the detection of oesophageal varices (OV) or large varices (LOV). TE: transient elastography.

Diagnostic performance of TE for the diagnosis of OV by Author	[54]	[55]	[56]	[57]	[47]
Number of pts	165	61 (47 cirrhotic)	150 (89 cirrhotic)	112	298 (70 cirrhotic)
Aetiology	Mixed (HCV predominant)	HCV	Mixed	Mixed	HCV
Prevalence OV	45%	64%	72%		36%
Proposed cutoffs for presence of OV/LOV	OV 13.1 LOV 19	17.6	OV 21.1 LOV 29.3	19.7	OV 21.5 LOV 30.5
Sensitivity (%)	95/91	90	84/81	87	76/77
Specificity (%)	43/60	43	71/61	70	78/85
PPV (%)	57/48	77		89	68/56
NPV (%)	91/95	66		66	84/94
AUROC	0.84/0.83	0.76	0.85/0.76	0.818	0.84/0.87

arterial and venous flow. It is considered the first-line imaging technique in patients with cirrhosis. Portal vein diameter, portal blood velocity and congestion index, spleen size, flow pattern in the hepatic veins, and the presence of abdominal portosystemic collaterals are all US parameters previously thought to have with prognostic significance but all with poor sensitivity and specificity [60]. One large study proposed prothrombin activity of less than 70%, portal vein diameter greater than 13 mm, and platelet count  $< 100 \times 10^9$  as noninvasive predictive tools to discriminate cirrhotic patients with and without oesophageal varices (OV) [61]. The ROC curve constructed from all possible combinations of these dichotomous variables initially looked promising with an area under the curve (AUC) value of 0.80. To assess the validity of this tool, the investigators used a matched second cohort where the positive predictive value was found to be significantly reduced [62]. A further validity study was repeated in another centre with a similarly poor sensitivity and specificity [63]. Thus, US has limited specificity and cannot replace endoscopy as a screening tool for large oesophageal varices [61, 63].

**2.3.2. CT.** Three recent studies suggest that multidetector CT is comparable to upper endoscopy in detecting small and large varices [64–66]. Only two of these studies were carried out prospectively [64, 65], and only one included a cost analysis [64]. In one of the previous studies, virtual oesophagography could be carried out using the CT scans, but this procedure requires time-consuming and invasive intubation of the oesophagus with a catheter for air insufflation [66]. CT was found to have approximately 90% sensitivity in the identification of oesophageal varices determined to be large on endoscopy, but only about 50% specificity. The sensitivity of CT detecting gastric varices was 87%. In addition, a significant number of gastric varices, perioesophageal varices and extraluminal pathology were identified by CT that were not identified by endoscopy. Use of CT as the initial screening modality for the detection of varices was significantly cost effective compared to endoscopy irrespective of the prevalence of large varices [64].

Patients overwhelmingly preferred CT over endoscopy in all three studies. One of the major limitations identified in all studies was the differing rates of interobserver agreement in variceal size of both modalities, with only one study finding agreement between radiologists being higher than between endoscopists [64]. How reproducible this model could, therefore, remain unproven. There are also major concerns over the risk of cumulative radiation exposure in prolonged screening programmes [67].

**2.4. Capsule Endoscopy.** New capsule endoscopy devices have been developed, specifically for use in the oesophagus, acquiring images from both ends of the device. Several studies have been performed, assessing the ability of these capsule endoscopy devices to detect any varices and identify large varices requiring primary prophylaxis [68–73]. Conventional OGD was used as the gold standard.

With regards to the detection of varices, sensitivity varied between 68–100%, and specificity 86–100% [70–72, 74]. In the largest study performed to date, 288 patients were recruited in a multicentre trial [68]. Conventional OGD identified OV in 180 patients (62.5%) and capsule endoscopy identified OV in 152 of these, giving a difference in diagnosing OV of 15.6% in favour of OGD. In 13 cases (14.5%), varices were identified by capsule but not confirmed by OGD. Overall agreement for detection of varices was 85.8%, with a sensitivity of 84%, specificity 88%, positive likelihood ratio 7.0, and negative likelihood ratio 0.18. With regard to the grading of varices, there was complete agreement on the grade in 79%. In differentiating between varices requiring treatment or not, the sensitivity, specificity, PPV, and NPV for capsule endoscopy were 78%, 96%, 87%, and 92%, respectively. Overall agreement on treatment decisions based on variceal size was 91% ( $\kappa = 0.77$ ). Other studies have correctly identified patients requiring primary prophylaxis in 74–100% of patients [69, 71, 72, 74]. 2 meta-analyses produced similar results with pooled sensitivities of 83% and 83.8% and pooled specificities of 85% and 80.5%, respectively for the diagnosis of oesophageal varices [75, 76].

Capsule endoscopy is reported to be feasible in 94–99% of patients with the main reasons for failure being because patients were unable to swallow the capsule or due to technical problems with the recording or function of the capsule. Adverse events have been reported in 0–1.4% of cases, including episodes of capsule retention necessitating removal. Tolerability of the capsule is found to be better than conventional OGD, with better preprocedure perception and postprocedure satisfaction. 26–83% patients prefer capsule endoscopy over conventional OGD in the studies performed to date [68–70, 72–74, 77].

With regard to cost-effectiveness, 2 studies have been performed, the first concluding that both screening methods are equivalent, the second that screening with capsule endoscopy followed by beta-blocker therapy may be cost-effective compared to OGD followed by beta-blocker therapy but is highly sensitive to local costs [78, 79].

Therefore in summary, capsule endoscopy is feasible in the majority of patients and with regard to patient preference, capsule endoscopy appears to be preferable to conventional endoscopy and may improve compliance with screening programmes, although this remains to be determined. The jury is still out with regard to cost but when it comes to performance, conventional OGD remains the gold standard.

### 3. The Future Approach to Noninvasive Detection of Oesophageal Varices

Cirrhosis and portal hypertension are characterized by the development of a hyperdynamic circulation with elevated cardiac output and stroke volume and reduced systemic vascular resistance [80]. These haemodynamic variables are independently associated with portal pressure and size of oesophageal varices [81–84]. Measurement is traditionally invasive, the thermodilution technique requiring introduction of a catheter into the pulmonary artery. A noninvasive method for assessing systemic haemodynamics may allow noninvasive detection of oesophageal varices. New techniques are now available that measure systemic haemodynamics noninvasively. The Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) is a non-invasive device that allows continuous beat-to-beat blood pressure and haemodynamic monitoring over a number of hours [85]. We have demonstrated the presence of the hyperdynamic circulation using this technique and shown significant differences in cardiac output and systemic vascular resistance according to the size of oesophageal varices. We have also shown significant correlation of these haemodynamic variables to the 1-year probability of variceal bleeding. Data as yet unpublished examining the predictive ability of noninvasive parameters has shown promising initial results, with an AUROC curve of 0.86 for cardiac output and 0.77 for peripheral vascular resistance for the diagnosis of large oesophageal varices. Optimal cutoffs for these haemodynamic parameters remain to be defined. Considering a cutoff of 7.06 L/min for cardiac output, this gave a sensitivity of 91% and a negative predictive value

of 93%, maintaining a diagnostic accuracy of 86%. Using a cutoff of 0.99 MU for peripheral vascular resistance gave a sensitivity of 91% and negative predictive value of 91%. These initial results require further investigation.

Proteomics is the large-scale study of proteins, particularly their structure and function and interactions in a biological system. Proteomics does not require prior knowledge of the proteins present and, therefore, is ideal to screen for the best biomarkers of disease. Promising results have been seen in patients with liver cirrhosis to search for markers of hepatic fibrosis [86–88] and has been demonstrated to be more accurate than fibroTest. The optimal biomarker needs to be able to predict clinically significant endpoints as well as liver histology, and so further research is needed to know whether proteomics will ever be useful in the noninvasive diagnosis of oesophageal varices.

The major significant endpoint with regard to varices is that of bleeding. The evidence shows that infection and variceal bleeding are related [89]. In experimental cirrhosis, bacterial products increase portal pressure by activating macrophages and releasing vasoconstrictive prostaglandins [90–92]. Soluble CD163 in serum is a new specific marker of macrophage activation. A recent study demonstrated that sCD163 is increased in cirrhosis, levels correlating with portal pressure, but that levels do not drop following reduction of portal pressure after transjugular intrahepatic portosystemic shunt [93]. Therefore, chronic activation of these cells may play a role in establishing and maintaining portal hypertension. Further work is needed to assess their potential not only as a noninvasive marker of oesophageal varices but of varices with the highest bleeding risk.

### 4. Conclusions

In conclusion, based on all the available evidence to date, upper GI endoscopy remains the gold standard for the diagnosis of oesophageal varices in cirrhotic patients despite its own limitations. Clinical, biochemical, and radiological parameters currently are not accurate enough to avoid screening endoscopy, due to the risks associated with missing patients with large oesophageal varices. A screening test must be simple and inexpensive, and therefore current promising tools such as CT scanning or capsule endoscopy which are highly acceptable to patients may not prove to be cost-effective or suitable for repeated measurement. Assessment of systemic haemodynamics and other serum markers may hold promise for the future, and more studies are needed to better understand and identify high risk groups, which may in time be facilitated by proteomic approaches.

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