Evaluation and Treatment of Esophageal Varices in the Cirrhotic Patient

Eyal Ashkenazi MD[1], Yulia Kovalev MD[1] and Eli Zuckerman MD[2]

[1]Liver Unit, Carmel Medical Center, Haifa
[2]Liver Unit, Carmel Medical Center affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: Portal hypertension is the leading cause of morbidity and mortality in liver cirrhosis. Complications of portal hypertension in cirrhotic patients include esophageal and gastric varices, portal hypertensive gastropathy, ascites, hepatorenal syndrome, hepatopulmonary syndrome and portopulmonary hypertension. The hepatic venous pressure gradient should be at least 10 mmHg for esophageal varices to appear, and more than 12 mmHg for acute esophageal variceal bleeding. This article reviews the pathophysiology responsible for portal hypertension and its complications, and the treatments used for esophageal varices in the setting of primary and secondary prophylaxis and during active bleeding.

IMAJ 2013; 15: 109–115

KEY WORDS: portal hypertension, esophageal variceal bleeding, primary prophylaxis, secondary prophylaxis, carvedilol, simvastatin, transjugular intrahepatic portosystemic shunt (TIPS)

Portal hypertension is a common clinical syndrome defined hemodynamically by pathologically elevated portal pressure. Elevated pressure indicates a pathologic process in the portal system. Portal hypertension can be classified anatomically as pre-hepatic, hepatic or post-hepatic, depending on the site of the pathology. The hepatic pathology can be further divided into pre-sinusoidal, sinusoidal or post-sinusoidal portal hypertension, according to different etiologies and different sites within the liver that can be affected by these etiologies [Table 1]. The most common cause of PHT in the western world is liver cirrhosis, accounting for 90% of cases. The most frequent cause of pre-hepatic PHT in the western world is portal vein thrombosis [1]. The most common cause of post-hepatic PHT is Budd-Chiari syndrome, which results from obstruction of the hepatic veins or the inferior vena cava in the area of these veins [2]. The etiology for portal hypertension differs in various parts of the world. For example, in Africa the most common cause of PHT is schistosomiasis, which begins as a pre-sinusoidal disease within the liver and may extend later into the liver parenchyma, causing fibrosis and sinusoidal hypertension.

PHT = portal hypertension

To assess portal pressure hemodynamically, the most accurate way is to measure the portal pressure directly. In practice, however, direct portal pressure measurement is not recommended because of potential complications. Instead, wedge hepatic pressure can be measured by placing a catheter in the hepatic vein, occluding it with a balloon, and measuring the post-occlusion pressure. This wedge pressure accurately reflects the intrasinusoidal portal pressure, especially in cirrhotic patients. Reducing the free hepatic pressure from the wedge hepatic pressure results in a gradient, termed the hepatic venous pressure gradient. Based on measurements of the wedge and free hepatic pressures, and the HVPG pressure, intrahepatic PHT can be divided into pre-sinusoidal, sinusoidal or post-sinusoidal PHT, as mentioned earlier. This classification is based on different hemodynamics for each sub-classification:

- **Pre-sinusoidal PHT:** Normal wedge pressure and free hepatic venous pressure (normal HVPG)

HVPG = hepatic venous pressure gradient

Table 1. Classification of portal hypertension

1. Pre-hepatic
Portal vein thrombosis (independent of cause), splenic vein tahrombosis, cavernous transformationof the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly

2. Intrahepatic
a. Pre-sinusoidal
Schistosomiasis, chronic viral hepatitis (HBV and HBC), cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson's disease, hemochromatosis, amyloidosis, remaining storage diseases, polycystic liver disease, infiltration of liver hilus (independent of cause), benign and malignant neoplasms
b. Sinusoidal
Liver cirrhosis (independent of cause), acute viral and alcoholic hepatitis, acute fatty liver of pregnancy
c. Post-sinusoidal
Venous occlusion disease, alcoholic hyaline sclerosis of central veins

3. Extrahepatic
Hepatic vein thrombosis (Budd-Chiari disease), inflammatory/neoplastic infiltration of the hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency

- **Sinusoidal PHT:** Elevated wedge pressure and normal free hepatic venous pressure (high HVPG)
- **Post-sinusoidal PHT:** Elevated wedge and free hepatic vein pressure (normal HVPG).

The next section will focus on portal hypertension in patients with liver cirrhosis, the resultant complications, especially esophageal varices, and the treatments that can be offered.

FROM PATHOPHYSIOLOGY TO THE CLINICAL SYNDROME

Cirrhotic PHT is a vascular disease that affects many body organs. The development of portal hypertension in patients with cirrhosis is a poor prognostic sign. The first event in the cascade of portal hypertension development is increased vascular resistance to portal blood flow. The reason is not merely mechanical; there is also a contributing dynamic component that is created by contracting portal myofibroblasts, activated hepatic stellate cells and vascular smooth cells in portal venules causing elevated vascular resistance. As a result, the pressure gradient between the portal vein and the hepatic vein is elevated to more than 5 mmHg. When the pressure gradient between the portal vein and the hepatic veins (HVPG) exceeds 10 mmHg, clinical pathology emerges. Such an elevation is defined as clinical significant portal hypertension. CSPHT already exists in about 60% of histologically proven, well-compensated cirrhotic patients [3].

Portal hypertension is defined as an elevated portal pressure and is the main cause of morbidity and mortality in liver cirrhosis

As a consequence of elevated liver resistance, systemic levels of vasoactive mediators are increased, including vasodilators such as nitric oxide on one hand, and vasoconstrictors such as thromboxane A2, endothelin, epinephrine, angiotensin and renin on the other. The interaction between these opposing vasoactive substances and their combined effect is responsible for some of the clinical phenomena caused by PHT:

- **Splanchic vascular bed:** Cirrhosis can cause splanchic vasodilatation, decreased responsiveness to vasoconstrictors, and formation of new blood vessels (angiogenesis), which contributes to the increase in splanchic blood flow and portosystemic collaterals [4] including esophageal and gastric varices. These varices tend to bleed when large enough or when portal pressure is high enough. Bleeding esophageal or gastric varices are the final and most important clinical event resulting from portal hypertension, and will be discussed in detail further on. Portosystemic collaterals and shunting are also involved in liver encephalopathy.
- **Systemic circulation:** Most patients with cirrhosis and portal hypertension have a hyperdynamic circulation, defined by a high cardiac output and index, low blood pressures, high blood volume but with low effective blood volume, and a low systemic vascular resistance [5]. Due to the low effective blood volume, volume receptors are stimulated (despite high blood volume), which leads to neurohormonal activation, salt and water retention in the renal system and, in many cases, ascites [6], and later on, renal failure, probably due to vasoconstricted glomerular afferent arterioles. Hepatic ascites can be infected spontaneously by bacteria colonizing the intestine, causing spontaneous bacterial peritonitis.

  Renal abnormalities can develop in the cirrhotic patient, especially if PHT already exists. There are many causes of renal failure in cirrhosis, but the most ominous and lethal is the hepatorenal syndrome, which is a functional renal disease (at least in the beginning) due to an imbalance between vasodilating and vasoconstricting factors in the systemic circulation. Due to this imbalance, vasoconstrictive factors become dominant and lead to afferent arteriole vasoconstriction in the renal glomeruli and deteriorating renal function that can lead to death within days to weeks [7].
- **Cardiopulmonary system:** Cirrhotic portal hypertensive patients often exhibit high cardiac output and index, as mentioned before. In addition, a long QT interval may also appear as part of other electrophysiological disturbances and tendency to cardiac arrhythmias. In later stages of decompensated cirrhosis, especially if accompanied by hepatorenal syndrome, cardiac output may in fact decrease for as yet unknown reasons [8]. These disturbances are called cirrhotic cardiomyopathy. In the pulmonary system, vasodilatation of pulmonary arterioles and shunting of blood to the left system, accompanied by ventilation/perfusion mismatch, is not uncommon. This phenomenon is defined as the hepatopulmonary syndrome. The opposite phenomenon is the portopulmonary syndrome, characterized by pulmonary artery hypertension due to high pulmonary vascular resistance for which there is no explanation to date. A possible cause is pulmonary endothelial dysfunction leading to vascular remodelling of the pulmonary system.
- **Blood abnormalities:** Leukopenia, thrombocytopenia and anemia are frequent findings in PHT patients, in part because of splenomegaly and hypersplenism and, in the case of hemoglobin and platelets, because of low production. It is well known that the thrombopoietin level is reduced or inappropriately low in PHT patients, which contributes to the thrombocytopenia that already exists due to the enlarged spleen and splenic sequestration [9].

CSPHT = clinical significant portal hypertension

DIAGNOSIS AND EVALUATION OF CIRRHOTIC PHT

HVPG MEASUREMENT

Since the practical definition of sinusoidal portal hypertension is based on an elevated pressure gradient between the sinusoidal pressure and the hepatic vein pressure, measuring this gradient is the gold standard method of diagnosis. Apart from being objective, HVPG serves as an independent tool to assess prognosis in cirrhotic patients with varying clinical conditions [10]. Elevated HVPG above 6 mmHg indicates sinusoidal portal hypertension. Further elevation above 10 mm Hg indicates CSPHT, as mentioned earlier.

ENDOSCOPY

There is a consensus that all cirrhotic patients should undergo an upper endoscopy as a screening tool for cirrhosis close to the time of diagnosis. This allows the addition of prophylactic therapy if esophageal or gastric varices are found. In a patient without varices on the initial assessment, endoscopy should be repeated approximately every 2 years since 5–10% of these patients will develop esophageal varices every year [3].

NON-INVASIVE CLINICAL LABORATORY AND IMAGING TECHNIQUES

Splenomegaly is the most frequently reported clinical sign with a correlation to portal hypertension. It can be found on physical examination, in upper abdominal ultrasonography or computed tomography. CT and ultrasound can also recognize abdominal venous collaterals, esophageal varices, liver nodularity, changes in size of the liver, enlarged portal vein diameter, and changes in portal vein flow velocity, which have been found to correlate with the existence of CSPHT [11]. Other measurements such as platelet count and a low platelets-to-spleen ratio probably reflect portal hypertension.

Transient elastography (FibroScan™, France) is a relatively new non-invasive technique developed to assess liver fibrosis. It appears that FibroScan is a useful tool to reach, or rule out, the diagnosis of CSPHT. Still, it is inaccurate in about 50% of patients with cirrhosis. Another disadvantage of FibroScan is that there is a poor correlation between the absolute Fibroscan result and the HVPG in patients with CSPHT (HVPG > 10 mmHg) [12].

FROM PATHOPHYSIOLOGY TO TREATMENT

As noted earlier, the first event in the cascade of portal hypertension development is increased vascular resistance to portal blood flow. This elevated vascular resistance can be treated by mechanical or pharmacological means. In addition, a second component of increased blood flow through the portal system, due to splanchic arteriolar vasodilatation, contributes to the elevated portal pressure. The reason for the splanchic arteriolar vasodilatation is probably increased release of some endogenous vasodilators, among which nitric oxide is best known [13]. Vasodilatation of the splanchic system is accompanied, as mentioned earlier, by hyperdynamic circulation, high cardiac output, low effective blood volume, hypervolemia, and salt and water reabsorbtion in the renal system, leading to ascites. Therefore, it is not surprising that treatment of PHT can be applied by mechanical TIPS (transjugular intrahepatic portosystemic shunt) or by pharmacological means (such as non-selective beta blockers, nitrates and diuretics). To complete the therapeutic profile, an arm of endoscopic therapy, such as variceal band ligation, even though it does not reduce the portal pressure, provides another tool to control and prevent rebleeding from esophageal varices in cirrhotic patients.

PREVENTION OF VARICES

At the time of diagnosis about 60% of cirrhotic patients have esophageal varices of different grades. In patients without varices, the rate of developing esophageal varices is about 5% annually. This is the rationale for the recommendation to screen for variceal varices every 2–3 years, and perhaps every year in high risk patients.

Experimental models demonstrated the ability of beta blockers to delay and attenuate the development of collaterals [14]. In clinical terms, however, beta blockers did not succeed in reducing or delaying the appearance of esophageal varices. [1]. Thus, the use of beta blockers as a preventive treatment in the cirrhotic patient without esophageal varices cannot be recommended.

The main treatments for esophageal varices are still beta blockers (with or without nitrates) and esophageal variceal band ligation, although carvedilol emerges as a treatment for esophageal varices in Child A cirrhotic patients

One approach that proved successful in preventing the progression of cirrhosis is to treat the basic etiology (weight loss in non-alcoholic steatohepatitis, steroids in autoimmune hepatitis, copper chelators in Wilson disease, abstinence from alcohol in alcoholic liver disease, and antiviral therapy in patients with hepatitis C virus infection). This proved successful in alcoholic cirrhosis where abstinence from alcohol decreased the complications of cirrhosis, and with hepatitis C virus cirrhosis where achieving a sustained virologic response correlated with reducing the portal pressure [15].

PRIMARY PREVENTION OF VARICEAL BLEEDING

In patients with existing esophageal varices, the annual rate of variceal bleeding is about 4%. Acute variceal bleeding is a medical emergency and a life-threatening event, with a mortality of about 25% within 6 weeks after the bleeding episode. Most of the deaths are related to liver failure and secondary complications such as hepatorenal syndrome, spontaneous

bacterial peritonitis and sepsis. Preventing or reducing the rate of variceal bleeding was therefore a target for many trials using pharmacological, mechanical and endoscopic treatments.

Beta blockers act by decreasing HVPG and were shown to attenuate the risk of variceal bleeding from 24% to 15% during a follow-up of 2 years [16]. The most studied beta blockers were propranolol and timolol and both were found to be effective. Mortality was reduced as well, but statistical significance was not achieved.

In the past it was recommended that only patients with medium to large varices be treated with beta blockers. Due to the fact that grading variceal size is subjective, and that small varices with red signs or in Child-Pugh class C cirrhotic patients have a similar bleeding rate as medium and large varices, it is now recommended that beta blockers be started as a preventive therapy in these groups as well [17].

It was recently shown in a hemodynamic trial that patients in whom HVPG decreased by 12% after receiving intravenous propranolol (responders) are at low risk of suffering a first episode of variceal bleeding or variceal rebleeding, compared with those not given propranolol (non-responders) [18]. There is still debate about which treatment strategy should be applied for the "non-responders" to i.v. propranolol, who, as shown in another trial, do not respond as well to EVL in terms of reducing the bleeding rate. More trials are needed to answer this question.

Transjugular intrahepatic portosystemic shunt (TIPS) seems a rational treatment in a selective group of cirrhotic patients with bleeding esophageal varices

The addition of nitrates to beta blockers as a primary prevention was assessed in two studies but did not show any advantage over beta blockers alone in reducing the rate of the first variceal bleeding in cirrhotic patients [19]. Therefore, adding nitrates cannot be recommended for this indication.

Endoscopic variceal band ligation, a procedure that includes banding varices with rubber rings endoscopically, was also the subject of numerous studies on preventing the first variceal bleeding episode. EVL was compared with beta blockers with regard to reducing the rate of first variceal bleeding events and was found as effective as beta blockers if only large randomized well-designed studies with more than 100 patients in each study were included [20]. Interestingly, patients treated with beta blockers suffered more side effects than those treated with EVL, but while adverse events of beta blockers were almost always reversible and usually mild, those of EVL were much more serious, including recurrent bleeding from banding-related variceal ulcers, even leading to death. This is the reason why EVL is not uniformly recommended by the author as a first-line treatment, unless beta blockers are not tolerated or contraindicated. Nonetheless, some physicians prefer band ligation as the first therapeutic step in primary prevention of variceal bleeding, relying largely on the fact that about 25% patients cannot tolerate beta blockers and that many do not take them without informing their physician; thus, the number of patients actually not treated with the drug may well be higher than we assume. Moreover, of those who do take beta blockers, more than 30% are early non-responders in terms of reducing HVPG [18], which reduces further the percentage of patients who benefit from beta blockers.

Combined treatment with EVL and beta blockers for primary prevention cannot be justified. A study that compared EVL plus beta blockers to EVL alone showed a small advantage over the combined treatment but at the cost of more side effects in the combined treatment arm [21]. Further studies are needed to clarify if there is a real advantage to this mode of combined treatment for primary prevention of variceal bleeding.

In the same context, there is an emerging debate on the preferred primary prevention therapy for patients who are candidates for liver transplantation. This population of patients is unique, since their liver disease is usually more advanced on the one hand, meaning that the first variceal bleeding is a real life-threatening event, probably with higher mortality. In addition, they might not need long-term medical treatment with beta blockers, if hopefully transplanted. Also, the fact that EVL doesn not actually reduce portal hypertension, (so, esophageal varices can theoreticaly develop again) does not have a long-term importance if the patient is scheduled for transplantation soon. On the other hand, EVL-related esophageal bleeding from a variceal ulcer might worsen these patients' medical condition dramatically, even making them unacceptable candidates for liver transplantation. Some trials assessed the effectiveness of EVL in this group, but with conflicting results [22,23]. The question of EVL or beta blockers for primary prevention of variceal bleeding in this group of patients will likely remain an open question, but it is suggested by the author that the time spent on the waiting list for liver transplantation in each center or country is an important consideration. In centers where the average waiting time for transplantation is long, beta blockers should be preferred, as in most cirrhotic patients. In centers where the bioavailability of donor organs is high, both beta blockers and EVL are considered reasonable options in view of the short waiting time for transplantation.

Recently, carvedilol, a non-selective beta blocker with an alpha blocker effect as well, was studied and proved to be more effective in reducing portal pressure than propranolol, in the set up of primary prophylaxis.. A study comparing carvedilol to EVL showed a lower rate of first variceal bleeding with carvedilol and no difference in mortality [24]. There is no study comparing carvedilol and beta blockers

EVL = endoscopic variceal band

in terms of clinical endpoints, but it seems that treatment with carvedilol in patients with variceal bleeding is a rational choice, especially if begun at a low dosage in patients with Child-Pugh class A cirrhosis.

Simvastatin emerges as a future drug for portal hypertension. Simvastatin was shown to reduce HVPG in patients with portal hypertension in both primary and secondary prophylaxis. Interestingly, the portal hypertension reduction effect was achieved due to reduced hepatic resistance and not to reduced hepatic blood flow [25]. A study evaluating the effect of simvastatin on cirrhotic portal hypertension in terms of clinical endpoints is already ongoing.

SECONDARY PREVENTION OF VARICEAL REBLEEDING

Patients surviving the first variceal bleeding have a 60% chance of rebleeding in the next year. Since variceal bleeding is a life-threatening event, with mortality of about 25% within the first 6 weeks, it is clear why a second prophylaxis is mandatory. Beta blockers were assessed in many randomized control trials and were shown to reduce the rate of rebleeding and mortality [16]. It was also shown that the combined effect of beta blockers and nitrates is stronger in reducing portal pressure. For this reason, the combination of these drugs was assessed in two trials on reducing the rebleeding rate, with conflicting results. No doubt the data on this combination therapy are not well proven. Nonetheless, since this combination was shown to be more effective than sclerotherapy in reducing the rebleeding rate [26], and since the adverse effects are not major, it is recommended that this combination treatment after the first variceal bleeding be considered, if there are no contraindications.

Sclerotherapy, the injection of a sclerosing agent into the varices, was shown to reduce the rebleeding rate but, due to unacceptable side effects such as esophageal stenosis, dysphagia and more, and due to the fact that endoscopic EVL proved more potent in reducing the rebleeding rate than sclerotherapy [27], sclerotherapy is no longer recommended as first-line endoscopic therapy in these patients.

The combined endoscopic and pharmacological treatment with EVL and beta blockers has been shown to reduce the rebleeding rate more than EVL alone [28]. For this reason, it is recommended that in a patient who survived the first variceal bleeding event, this combined treatment should be initiated as a first-line therapy, with the addition of nitrates as well. The varices should be banded in a few separate gastroscopy sessions until disappearance of all varices, or at least the not significant varices. The rate of banding sessions is a question of debate, but it is accepted that an interval of 2 weeks to 1 month is reasonable.

TIPS is a very effective way to reduce variceal rebleeding after the first variceal bleeding. Until recently TIPS did not demonstrate superiority over conventional therapy with propranolol and EVL in terms of survival and was associated with higher encephalopathy rates when compared to conventional treatment. Recent evidence shows that in a select group of cirrhotic patients with first variceal bleeding TIPS emerges as an acceptable treatment. When measuring the HVPG of cirrhotic patients with first esophageal variceal bleeding, a value > 20 mmHg is significantly correlated with a high risk of short-term rebleeding [29]. It was recently shown that when placed wihin the first 3 days after the bleeding episode TIPS reduced rebleeding rates, improved 2 year survival, and was associated with a reduced risk of hepatic encephalopathy in a select group of patients with cirrhosis Child-Pugh class B or C with acute esophageal bleeding for 3 days after the bleeding episode [30]. This new evidence may shift the pendulum towards acceptance of TIPS as a therapeutic procedure for the first esophageal bleeding episode in a select group of cirrhotic patients.

Finally, it is important to remember that the only definitive therapy to prevent variceal rebleeding in a cirrhotic patient is liver transplantation, so every patient with a history of esophageal variceal bleeding should be evaluated, and if found suitable, should be offered this treatment option.

TREATMENT OF ACUTE ESOPHAGEAL VARICEAL BLEEDING

Acute variceal bleeding is a medical emergency and a life-threatening event with a mortality of about 25%. The treatment of acute variceal bleeding should be a combination of treatments given by hepatologists, gastroenterologists, anesthesiologists and infectiologists. A good cooperation between these experts might lead to a better outcome for the patient.

The patient with variceal bleeding should be treated in the intensive care unit. The first step is to restore the patient's hemodynamic status and ensure that major organs are not affected by the continuous bleeding. The patient should be given full oxygenation and, if unstable hemodynamically, should receive fluid resuscitation. Anemia should be corrected to a level of about 25% hematocrit. A correction to a higher level is not recommended due to the risk of rebleeding in these patients because of volume overload. A nasogastric tube should be inserted into the stomach for drainage, as well as a urinary catheter to the bladder to measure urine output. The patient should be fully monitored and if possible should have a central vein catheter to assess his/her hemodynamic status accurately. Patients with reduced conscious level are at risk of aspiration and should be intubated and ventilated. Coagulation disturbances, which are fairly common in these non-compensated cirrhotic patients, should be corrected with fresh frozen plasma.

There is an increased rate of infections in patients suffering from acute variceal bleeding, with pneumonia, spontaneous bacterial peritonitis and urinary tract infections being the most common. Antibiotic therapy should be started on a preventive basis as it was shown to reduce the rate of infections, reduce

TIPS = transjugular intrahepatic portosystemic shunt

the rebleeding rate and improve survival in these patients [31]. Usually quinolones are the antibiotics of choice, but in patients with spontaneous bacterial peritonitis in the past or patients with Child-Pugh class C, ceftriaxone should be introduced due to its superiority [32].

About 50% of all esophageal variceal bleeding episodes stop spontaneously [26], but the rebleeding rate is high with about 50% of patients experiencing a second episode, usually within 2 weeks after the first episode. A second episode of bleeding puts the patient at a high mortality risk and is thus the reason for starting pharmacologic therapy as soon as possible. Pharmacologic therapy in acute esophageal variceal bleeding is based on the pathophysiology of portal hypertension. The target is to reduce the portal pressure by reducing the flow to the portal system.

Terlipressin, an analogue of vasopressin, has an effect of relatively selective splanchic vasoconstriction and is the drug of choice for this purpose, since it was shown to improve outcome in these patients in terms of bleeding control and survival [33]. Therapy with terlipressin should be started as soon as possible, even if variceal bleeding is only suspected and not proven. The starting dosage is 2 mg every 6 hours for the first 48 hours and can be reduced later to half the dose for the next 3 days. It is important to continue therapy for 5 days even after the bleeding has stopped, due to the high rate of rebleeding in these patients. Side effects of terlipressin are usually minor. Rarely, peripheral or myocardial ischemia and abdominal pain may occur.

Another therapeutic option is to start somatostatin at a starting dose of 250 μg followed by a 250 μg/hour infusion, which is maintained until 24 hours bleed free is achieved. Treatment can be prolonged to 5 days to prevent rebleeding. It is worth noting that despite the effect of somatostatin on bleeding control, no impact on survival was shown [16]. For this reason somatostatin is recommended as a second-line therapy for this condition.

Octreotide, a somatostatin analogue, is another option for second-line therapy for variceal bleeding. The dose is an initial bolus of 50 μg, followed by 25 μg/hour for up to 5 days. The efficacy of octreotide to stop variceal bleeding is controversial but was superior to sclerotherapy in preventing early rebleeding [34].

EVL and sclerotherapy were both validated as effective treatments for the control of esophageal variceal bleeding. EVL was more effective than sclerotherapy [35] and is associated with fewer side effects. Therefore, EVL should be the first-line endoscopic therapy. Sclerotherapy can be a therapeutic option in cases where EVL is not available. Endoscopy should be performed early after admission to hospital, assuring that the patient was resuscitated and is stable hemodynamically.

The recommendation for the initial treatment is to combine medical and endoscopic therapy, starting terlipressin immediately on admission to hospital, followed as soon as possible by EVL after initial resuscitation. Several trials have demonstrated that starting a vasoactive drug before endoscopic therapy improves bleeding control and reduces the rebleeding rate [36,37].

Balloon tamponade is not an ideal therapeutic option and should be used only in the event of massive bleeding. The balloon achieves hemostasis in about 60–90% of cases but cannot be in place for more than 24 hours. After the balloon is removed, bleeding starts in at least 50% of patients. In addition, balloon tamponade might cause severe side effects such as esophageal rupture. This is why this option is used only as a bridge until a more definitive therapy such as TIPS [38].

TIPS and surgical shunts are another option for a salvage therapy in the "resistant bleeder." TIPS is preferred over surgical therapy due to the advanced stage of cirrhosis in these patients. Still, it should be kept in mind that the rate of encephalopathy after TIPS placement is high and, when inserting TIPS in a patient with Child-Hugh C cirrhosis, liver failure almost always occurs. Thus, a liver transplantation should be planned for these patients, if possible, after placing the TIPS.

Despite all of the above mentioned treatments for portal hypertensive complications in the cirrhotic patient, it is important to remember that the only definitive treatment for portal hypertension due to liver cirrhosis is liver transplantation.

Corresponding author:
Dr. E. Ashkenazi
Liver Unit, Carmel Medical Center, Haifa 34362, Israel
Phone: (972-4) 825-0052
email: eyalas@clalit.org.il, ashken11@gmail.com

References

1. Valla DC, Condat B. Portal vein thrombosis in adults: pathophysiology, pathogenesis and management. *J Hepatol* 2000; 32: 865-71.
2. Plessier A, Sibert A, Consigny Y, et al. Aiming at minimal invasiveness as a therapeutic strategy for Budd Chiari syndrome. *Hepatology* 2006; 44: 1308-16.
3. Groszman RJ, Garcia-Tsao G, Bosch J, et al. Beta blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; 353: 2254-61.
4. Fernandez M, Vizzuti F, Garcia Pagan JC, Rodes J, Bosch J. Anti VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. *Gastroenterology* 2004; 126: 886-94.
5. Bosch J, Abraldes JG, Groszman RJ. Current management of portal hypertension. *J Hepatol* 2003; 38: S54-68.
6. Schrier RW, Arroyo V, Bernardi M, Eppstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; 8: 1151-7.
7. Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. *Lancet* 2003; 362: 1819-27.
8. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005; 42: 439-47.
9. Rois R, Sangro B, Herrero I, Quiroga J, Prieto J. The role of thrombopoietin in thrombocytopenia of patients with liver cirrhosis. *Am J Gastroenterol* 2005; 100: 1311-16.
10. Bosch J, Abraldez JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol* 2009; 6: 573-82.

11. Zoli M, Iervese T, Merkel C, et al. Prognostic significance of portal hemodynamics in patients with compensated cirrhosis. *J Hepatol* 1993; 17: 56-61.
12. Vizutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV related cirrhosis. *Hepatology* 2007; 45: 1290-7.
13. Pizcueta MP, Pique JM, Bosch J, Whittle BJ, Moncada S. Effects of inhibiting nitric oxide biosynthesis on the systemic and splanchic circulation of rats with portal hypertension. *Br J Pharmacol* 1992; 105: 184-90.
14. Sarin SK, Groszman RJ, Mosca PG, et al. Propranolol ameliorates the development of porto-systemic shunting in a chronic murine schistosomiasis model of portal hypertension. *J Clin Invest* 1991; 87 (3): 1032-6.
15. Rincon C, Ripoli C, Lo lacono O, et al. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. *Am J Gastroenterol* 2006; 101 (10): 2269-74.
16. D'amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence based approach. *Semin Liver Dis* 1999; 19 (4): 475-505.
17. De Francis R. Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; 53: 762-8.
18. La Mura V, Abraldes JG, Raffa S, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol* 2009; 51 (2): 279-87.
19. Garcia-Pagan JC, Morillas R, Banares R, et al. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate for prevention of first variceal bleed: a double blind RCT. *Hepatology* 2003; 37 (6): 1260-6.
20. Gludd LL, Klingenberg S, Nikolova D, Gludd C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systemic review of randomised trials. *Am J Gastroenterol* 2007; 102 (12): 2842-8; quiz 2841, 2849.
21. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol* 2005; 100 (4):797-804.
22. Lim EJ, Gow PJ, Angus PW. Endoscopic variceal ligation for primary prophylaxis of esophageal variceal hemorrhage in pre-liver transplant patients. *Liver Transpl* 2009; 15 (11): 1508-13.
23. Norberto L, Polese L, Cillo U, et al. A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. *Liver Transpl* 2007; 13 (9): 1272-8.
24. Tripathy D, Ferguson JW, Kochar N, et al. Randomised controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009; 50: 825-33.
25. Abraldes J.G, Abillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized control trial *Gastroenterology* 2009; 136: 1651-8.
26. Villanueva C, Balanzo J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal bleeding. *N Engl J Med* 1996; 334: (25): 1624-9.
27. Garcia-Pagan JC, Bosch J. Endoscopic band ligation in the treatment of portal hypertension. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 526-35.
28. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective randomized trial. *Hepatology* 2000; 32: 461-5.
29. Moithino E, Escorsell A, Bandi JC, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; 117: 626-31.
30. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med* 2010; 362: 2370-9.
31. Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; 29: 1655-61.
32. Farnandez J, Ruiz-Del-Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxine in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006; 131: 1049-56.
33. Ioannou GN, Doust J, Rockey DC. Systemic review: terlipressin in acute esophageal variceal hemorrhage. *Aliment Pharmacol Ther* 2003; 17: 53-64.
34. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal bleeding: a meta-analysis. *Gastroenterology* 2001; 120: 946-54.
35. Lo GH, Lai KH, Cheng JS, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology* 1997; 25: 1101-4.
36. Levacher S, Letoumelin P, Pateron D, Blaise M, Lapandry C, Pourriat JL. Early administration of terlipressin plus glycerol trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; 346: 865-8.
37. Villanueva C, Ortiz J, Sabat M, et al. Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal variceal bleeding: a prospective randomized trial. *Hepatology* 1999; 30: 384-9.
38. Goykhman Y, Ben Haim M, Rosen G, et al. Transjugular intrahepatic portosystemic shunt: current indications, patient selection and results. *IMAJ Isr Med Assoc J* 2010; 12 (11): 687-91.

Capsule

Lymph node T cell responses predict the efficacy of live attenuated SIV vaccines

Live attenuated simian immunodeficiency virus (SIV) vaccines (LAVs) remain the most efficacious of all vaccines in non-human primate models of human immunodeficiency virus and AIDS, yet the basis of their robust protection remains poorly understood. Fukazawa et al. show that the degree of LAV-mediated protection against intravenous wild-type SIVmac239 challenge strongly correlates with the magnitude and function of SIV-specific, effector-differentiated T cells in the lymph node but not with the responses of such T cells in the blood or with other cellular, humoral and innate immune parameters. The authors found that maintenance of protective T cell responses is associated with persistent LAV replication in the lymph node, which occurs almost exclusively in follicular helper T cells. Thus, effective LAVs maintain lymphoid tissue-based, effector-differentiated, SIV-specific T cells that intercept and suppress early wild-type SIV amplification and, if present in sufficient frequencies, can completely control and perhaps clear infection, an observation that provides a rationale for the development of safe, persistent vectors that can elicit and maintain such responses.

Nature Med 2012; 18: 1637

Eitan Israeli

"There may be times when we are powerless to prevent injustice, but there must never be a time when we fail to protest"

Elie Wiesel (born 1928), Romanian-born Jewish-American writer, professor, political activist, Nobel Laureate, and Holocaust survivor