Esophageal varices

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Esophageal varices is an eventual event in most cirrhotic patients because of portal hypertension. Bleeding from esophageal varices usually occurs in only one third of cases. Treatment of portal hypertension is directed towards decreasing variceal flow, which is achieved by reducing either portal venous inflow or resistance to portal outflow.

Anatomical background

The portal vein, formed by the confluence of the superior mesenteric vein and the splenic vein , drains the stomach, the large and small intestine, the pancreas, and the spleen. An important feature of this system is that a number of its tributaries also communicate with the systemic circulation. These include the intrinsic and extrinsic veins of the gastroesophageal junction; hemorrhoidal veins of the anal canal; paraumbilical veins and the recanalized falciform ligament; the splenic venous bed and the left renal vein; and the retroperitoneum.

In portal hypertension when the portal pressure exceeds the systemic venous pressure, these venous collaterals dilate and allow portal venous blood to return to the systemic circulation. Clinically, the most significant collaterals are the intrinsic veins of the gastroesophageal junction, as they are the most likely to bleed.

The veins of the gastroesophageal junction are classified as intrinsic, extrinsic, and venae comitantes. The intrinsic veins form a subepithelial and submucosal plexus starting at the gastric cardia (upper stomach) and running the length of the esophagus. In healthy persons, these veins drain into the extrinsic plexus through perforating veins 2 to 3 cm above the gastroesophageal junction. Flow through the perforating veins is unidirectional toward the extrinsic plexus and systemic circulation. When portal hypertension develops, however, the valves of the perforating veins become incompetent and allow reversal of flow from the extrinsic to the intrinsic system.

Varices of the gastroesophageal junction usually are classified by location as esophageal or gastric. Both are classified further aiming at detection of the highest risk of bleeding

Esophageal

Small, straight
Enlarged, tortuous; occupy less than one third of the lumen
Large, coil-shaped; occupy more than one third of the lumen (higher risk of bleeding)

Gastric

In continuity with esophageal varices

- Along lesser curve (2 to 5 cm long)
- Along greater curve extending toward the fundus

Isolated

- In the fundus (higher risk of bleeding)
- Elsewhere in the stomach

Pathophysiology of portal hypertension

Portal pressure can be measured only angiographically and is expressed in terms of hepatic venous pressure gradient (HVPG). HVPG is the difference between the *wedged hepatic venous pressure* (reflection of sinusoidal pressure) and the *free hepatic venous pressure* (correction for the effects of intra-abdominal pressure eg, tense ascites). Normally, HVPG is less than 5 mm Hg. Any value greater than 5 mm Hg is considered as hypertension. However, significant varices form only if HVPG is > 12 mm Hg . This explains why varices may not be present in every patient with clinical signs of portal hypertension.

Portal pressure is directly related to portal venous inflow and the degree of outflow resistance; it can be expressed in terms of Ohm's law as follows:

Portal pressure = portal venous inflow X outflow resistance

The initiating event in the development of portal hypertension is increased resistance to portal outflow. In cirrhosis, portal hypertension is aggravated by the increase in the portal venous inflow due to splanchnic vasodilation. When portal pressures rise, blood flow is diverted to venous collaterals that dilate to form varices. The likelihood that any one varix will rupture and bleed depends on its wall tension. This means that a large, long varix with a high flow rate and a thin wall is most likely to rupture and bleed. The decrease in portal hypertension is achieved by reducing either portal venous inflow (eg, by splanchnic vasoconstriction) or resistance to portal outflow (eg, by creation of a shunt).

Causes of portal hypertension

Presinusoidal
Extrahepatic causes

- Portal vein thrombosis
- Extrinsic compression of the portal vein
- Cavernous transformation of the portal vein

Intrahepatic causes

- Sarcoidosis
- Primary biliary cirrhosis
- Hepatoportal sclerosis
- Schistosomiasis

Sinusoidal
Cirrhosis
Alcoholic hepatitis

Postsinusoidal
Budd-Chiari syndrome (hepatic vein thrombosis)
Veno-occlusive disease
Severe congestive heart failure
Restrictive heart disease

Varices develop eventually in most patients with cirrhosis, but only one third of them experience variceal bleeding. It is essential to identify and treat those patients at highest risk because each episode of variceal hemorrhage carries a 20% to 30% risk of death, and up to 70% of patients who do not receive treatment die within 1 year of the initial bleeding episode.

Risk determinants for variceal bleeding

Portal pressure

- HVPG >12 mm Hg

Varix size and location

- Large esophageal varices
- Isolated cluster of varices in fundus of stomach

Variceal appearance on endoscopy ("red signs")

- Red wale marks (longitudinal red streaks on varices)
- Cherry-red spots (red, discrete, flat spots on varices)
- Hematocystic spots (red, discrete, raised spots)
- Diffuse erythema

Degree of liver failure

- Child-Pugh class C cirrhosis*

Ascites

- Tense ascites

After an acute variceal hemorrhage, bleeding resolves spontaneously in 50% of patients. Bleeding is least likely to stop in patients with large varices and a Child-Pugh class C cirrhotic liver. Once the bleeding stops, patients remain at increased risk of rebleeding for about 6 weeks; such risk is greatest during the first 48 hours after hemorrhage.

Factors associated with early rebleeding include age over 60 years, renal failure, and severe initial bleeding defined by hemoglobin of less than 8 g/dL at presentation.

Risk factors for late rebleeding are severe *liver failure, continued alcohol abuse, large variceal size, and hepatocellular carcinoma.*

Management of variceal hemorrhage

This will be discussed under two categeories: Prophylaxis and Treatment. Prophylaxis is either primary (prevent bleeding) or secondary (guard against rebleeding).

Primary Prophylaxis: prevention of the initial bleeding episode. This can be achieved by the use of pharmacotherapy esp non-selective beta blockers (Inderal). Endoscopic injection of sclerosants was shown to increase the risk of bleeding, perforation, pleural effusion, strictures and overall increase in the mortality, so it has been refused as a primary prophylaxis. Surgical shunting was used for long as the first line of treatment in such patients but now it has been condemned as a primary prophylactic measure due to its high incidence of encephalopathy. Little is known about the effectiveness of either radiologically placed shunts or endoscopic variceal ligation.

Non selective beta blockers act through $beta_2$ blockade, allowing unopposed alpha-adrenergic activity to constrict mesenteric arterioles and reduce portal venous flow, also decrease cardiac output, further limiting flow to the splanchnic circulation.

The beta-blocker dose is adjusted to decrease the resting heart rate by 25% from its baseline, but not to less than 55 to 60 beats/min. In clinical trials, 10 to 480 mg of propranolol daily, in divided doses, or 40 to 320 mg of nadolol daily in a single dose was used.

Nitrates: At usual doses, nitrates are vasodilators that decrease cardiac output by reducing venous return. Systemic vasodilation also decreases post-sinusoidal resistance and portal pressure. At high doses, nitrates cause arterial dilation and hypotension, leading to reflex splanchnic vasoconstriction and further decreases in portal pressures.
Nitrates are used in cases of non-responsiveness to beta blockers, contra-indication to beta blockers and side effects of beta blockers.

Conclusion policy
All patients with cirrhosis should undergo endoscopy to screen for varices. The optimum interval for subsequent screening is accepted to be every 2 to 3 years. Patients with large varices or endoscopic signs for increased risk of bleeding, or both, should be treated with nonselective beta blockers.

Acute variceal hemorrhage
Management of active variceal bleeding must aim at: 1-hemodynamic resuscitation, 2-prevention and treatment of complications, 3- control of bleeding.

Hemodynamic resuscitation requires administration of blood products and crystalloid (overtransfusion may cause rebound portal hypertension that leads to rebleeding). Hematocrit must not be less than 30%. Clotting factors often need to be determined as well. Platelet transfusions are reserved for counts below 50,000/mL in an actively bleeding patient.

Complications related to bleeding or its treatment can substantially increase the risk of death in each episode. Thus, patients with altered mental status and those with massive hematemesis should be intubated for airway protection; prevention of aspiration pneumonia cannot be overemphasized. Because patients with acute variceal hemorrhage are often volume-depleted, nephrotoxins (eg, aminoglycosides, nonsteroidal anti-inflammatory drugs) should be avoided to prevent renal failure. Patients should be monitored for abnormalities such as hypocalcemia and hyperkalemia, which are common during significant blood product transfusions. Because bacteremia often occurs during endoscopic sclerotherapy, patients with valvular heart disease and those with ascites should receive antibiotics at the time of the procedure to prevent subacute bacterial endocarditis and spontaneous bacterial peritonitis, respectively.

Therapeutic endoscopy is the definitive treatment for active variceal hemorrhage. However, when endoscopy is unavailable or delayed, pharmacologic agents play an important role in altering the course of a bleeding episode.

Vasopressin: directly constricts mesenteric arterioles and decreases portal inflow, thus decreasing portal pressure and controlling as many as 60% to 75% of variceal bleeding episodes. However, it does not increase the survival rate and may actually increase the mortality rate because of vasoconstrictive effects on other organs (eg, heart, intestine). Nitroglycerin (Nitro-Bid IV, Tridil) given concomitantly alleviates some of the vasoconstriction; this combination is better than vasopressin alone for controlling acute bleeding.

Octreotide acetate: Octreotide acetate (Sandostatin) is a synthetic, long-acting analogue of somatostatin. By inhibiting the release of vasodilatory hormones (eg, glucagon), it indirectly causes splanchnic vasoconstriction and decreased portal flow. Because it has fewer side effects than vasopressin, octreotide has become the drug of choice in the pharmacologic management of acute variceal bleeding. Unfortunately, like vasopressin, it does not increase the survival rate

Endoscopic therapy: **Endoscopic sclerotherapy remains first-line therapy for active variceal bleeding**. A sclerosant is injected into a varix under direct vision during endoscopy. This causes tissue edema and mechanical compression followed by inflammation, variceal thrombosis, fibrosis and, finally, obliteration.

Complications include bleeding ulcers, dysphagia due to stricture formation, and pleural effusions. Serious but rare problems are aspiration pneumonia, acute respiratory distress syndrome, and esophageal perforation.

The addition of octreotide to sclerotherapy, however, resulted in significant improvement in early bleeding control .

Endoscopic variceal ligation appears to be emerging as a viable alternative to sclerotherapy, mainly because of fewer complications and similar efficacy in bleeding control . Elastic bands are placed around varices using a device attached to the end of the endoscope. Ischemic necrosis, thrombosis, and fibrosis ensue, eradicating the varix. Concomitant use of octreotide may further decrease rebleeding rates.

Transjugular intrahepatic portosystemic shunt: TIPS is an angiographically created shunt between hepatic and portal veins that is kept open by placement of a fenestrated metal stent. It effectively decompresses the portal system, controlling active variceal bleeding over 90% of the time and achieving a mortality rate of less than 10%, even in critically ill patients . Immediate complications include *secondary bleeding* and, in 20% of cases, worsening *encephalopathy*. The most common long-term complications are *stent stenosis* or *occlusion* that requires balloon angioplasty. TIPS is primarily used as rescue therapy when pharmacologic and endoscopic treatment of acute bleeding is unsuccessful (11).

Causes of recurrent portal hypertension and rebleeding after TIPS

Stent dysfunction

- Thrombosis
- Retraction
- Displacement
- Stenosis

Severe right-sided heart failure

Hemobilia

Persistent gastric varices

- Associated with spontaneous splenorenal collaterals
- Associated with massive splenomegaly

Other considerations: If bleeding persists (or recurs within 48 hours of the initial episode) despite pharmacologic therapy and two endoscopic therapeutic attempts at least 24 hours apart, patients should be considered for salvage therapy. Depending on local expertise and the patient's condition, either TIPS or surgical treatment (transection of esophageal varices and devascularization of the stomach, portacaval shunt, or liver transplantation) should be considered.

In general, TIPS is preferred for high-risk patients because of its lower complication rates and ability to act as a bridge to liver transplantation. When bleeding occurs more

than 48 hours after the initial episode, a second attempt at endoscopic therapy should be made.

Secondary prophylaxis
Without additional therapy, a patient who has survived an episode of variceal hemorrhage has an overall risk of rebleeding that approaches 70% at 1 year. The clinical course often is one of recurrent hemorrhage that leads to hepatic decompensation and death . Prevention of recurrent hemorrhage is therefore the key to survival in a patient with varices. All of the treatments previously described also are available for secondary prophylaxis.

Endoscopic therapy: Sclerotherapy is the most extensively studied treatment for prevention of recurrent variceal hemorrhage. It decreases the risk of rebleeding (70%) and death. More recently, a series of controlled trials has shown endoscopic variceal ligation to be superior to sclerotherapy in time to variceal obliteration, number of complications, number of rebleeding episodes, and survival rate .

As a result, band ligation has replaced sclerotherapy as first-line treatment in secondary prevention of variceal hemorrhage.

Banding is carried out every 2 to 3 weeks until obliteration. All the complications of sclerotherapy previously described can occur during these sessions. Most episodes of breakthrough bleeding occur before the varices are completely obliterated. Because varices tend to recur over time, surveillance endoscopy must be performed every 6 to 12 months so that banding can be reinstituted as needed.

Shunts: Patients who have had TIPS are significantly less likely to bleed than those who underwent endoscopic therapy. Their survival rate, however, is not improved (and may be poorer), and they have to contend with numerous procedure-related complications (eg, hematomas, liver capsule rupture, pulmonary edema) and long-term complications (eg, encephalopathy, liver failure, hemolysis, TIPS stenosis).

TIPS therefore is used primarily as salvage therapy in the 40% to 50% of patients who have failed adequate endoscopic and pharmacologic therapy. Surgical shunts also are excellent at controlling active bleeding and preventing rebleeding, but at the expense of a significantly increased risk of death (especially in patients with advanced disease) when compared with endoscopic therapy.

Liver transplantation is the only effective treatment for both portal hypertension and liver failure and should be considered in any patient who survives a variceal bleeding episode.

Summary

Variceal hemorrhage is one of the most serious complications of portal hypertension. Nonselective beta blockers are the treatment of choice for prevention of the first bleeding episode. Active bleeding is managed with octreotide and endoscopic sclerotherapy. TIPS and shunt surgery are reserved for those in whom octreotide and endoscopic surgery have failed. Endoscopic band ligation should be used for

prevention of recurrent bleeding. If endoscopic band ligation fails, patients can be offered TIPS or surgical therapy; they should be evaluated for liver transplantation.