Screening for Varices and Prevention of Bleeding

This is a PDF version of the following document:
Module 3: Management of Cirrhosis-Related Complications
Lesson 3: Screening for Varices and Prevention of Bleeding

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Pathophysiology and Portal Dynamics

Pathogenesis of Portal Hypertension

In patients with cirrhosis, portal hypertension results from both an increase in resistance to portal blood flow and enhanced portal blood flow. The increased resistance in the liver results from architectural distortion due to fibrosis and regenerative nodules combined with increased intrahepatic vasoconstriction due to decreased endogenous nitric oxide production and endothelial dysfunction. In the presence of angiogenic factors and increased nitrous oxide production in the splanchnic vascular bed, splanchnic arteriolar vasodilatation and increased cardiac output increase portal venous blood inflow.[1]

Portosystemic Collaterals

Collaterals develop in response to the portal hypertension at sites of communication between the portal and systemic circulations. In comparison to other collaterals, gastroesophageal varices are important due to their risk of rupture and bleeding.

Hepatic Venous Pressure Gradient

The hepatic venous pressure gradient (HVPG) is a measure of portal (sinusoidal) pressure and is obtained by catheterization of a hepatic vein via the jugular or femoral vein. The free hepatic vein pressure is subtracted from the wedged hepatic vein pressure to calculate HVPG, which is normally 3 to 5 mmHg, and an elevated value indicates an intrahepatic cause of portal hypertension. The HVPG predicts the risk of developing varices and overall prognosis (Figure 1).[1,2] It can also be followed to monitor response to therapy and progression of liver disease. An HVPG value of 10 or greater indicates the patient has developed clinically significant portal hypertension and varices may develop when the HVPG is greater than or equal to 10 to 12 mmHg. The goal of therapy is to reduce the HVPG to less than 12 mmHg or decrease by 20% from baseline values.[3] Due to the invasive nature of the procedure and operator variability, its use is still not widespread in the United States for prognostic or therapeutic monitoring purposes. Clinically, it is used to diagnose portal hypertension and to identify the site of obstruction (prehepatic, intrahepatic, or posthepatic). It is also used to estimate the risk of liver failure following hepatic resection in patients with compensated chronic liver disease.
### Indications and Methods for Variceal Screening

#### Variceal Screening

Varices are present in 30 to 40% of patients with compensated cirrhosis and in 60% of patients with decompensated cirrhosis (at the time of diagnosis of cirrhosis). Upon diagnosis of cirrhosis, screening esophagogastroduodenoscopy (EGD) is recommended to evaluate for the presence of gastroesophageal varices.[3] The EGD evaluation for varices will determine whether the patient should receive prophylaxis for variceal bleeding with a nonselective beta-blocker. Less invasive markers for the presence of varices, such as platelet count, spleen size, and liver stiffness measurement, do not accurately predict the presence of varices. If no varices are found (Figure 2), an EGD should be repeated in 2 to 3 years. If esophageal varices are found (Figure 3), they should be classified into one of two grades: small (less than or equal to 5 mm) or large (greater than 5 mm).

#### Special Circumstances

Individuals already taking a nonselective beta-blocker, such as propranolol (Inderal) or nadolol (Corgard), do not need to undergo screening EGD. Those patients taking a selective beta-blocker, such as metoprolol (Lopressor) or atenolol (Tenormin), for other medical reasons should consider switching to a nonselective beta-blocker or carvedilol (Coreg).

#### Alternative Methods

Since performing an EGD requires conscious sedation of the patient, use of wireless video capsule endoscopy (patient swallows a capsule the size of large pill with a video camera on both ends) may be a reasonable alternative in patients who are not candidates for sedation or who refuse traditional endoscopy. Video capsule endoscopy, however, is not considered a first-line screening modality.
Pre-Primary and Primary Prophylaxis of Variceal Bleeding

Patients with compensated cirrhosis without gastroesophageal varices typically develop varices at a rate of 5 to 10% per year. In addition, patients with small esophageal varices progress to large varices at a rate of 8% per year. It is important to decrease the risk of variceal hemorrhage, which occurs at a rate of 5 to 15% per year, with the highest rates in those with large varices, decompensated cirrhosis, or red wale markings on the varices. The term pre-primary prophylaxis refers to prevention of the development of varices in patients with portal hypertension. Primary prophylaxis is defined as prevention of variceal hemorrhage in patients with known esophageal varices but no history of variceal hemorrhage. Secondary prophylaxis describes variceal hemorrhage prevention measures for patients with a known history of variceal hemorrhage.

Absence of Varices

For patients with absence of varices, pre-primary prophylaxis is not recommended to prevent the development of varices. In patients with compensated cirrhosis (i.e. absence of ascites, encephalopathy, jaundice and varices), a large multi-center, placebo-controlled, double-blinded trial showed that nonselective beta-blockers do not prevent the development of varices in the absence of demonstrable effect on HVPG and are associated with unwanted side effects.\[4\] Individuals with compensated cirrhosis and absence of varices should undergo screening EGD every 2 to 3 years.

Small Esophageal Varices

In patients with small esophageal varices (diameter of 5 mm or less) (Figure 4) that have not bled, nonselective beta-blockers may slow down variceal growth, but have not been shown to confer a survival advantage. Given the potential for side effects, the use of nonselective beta-blockers for primary prophylaxis in patients with small esophageal varices is generally reserved for those at higher risk of hemorrhage, namely those with red wale marks (red marks or red spots) on varices (Figure 5) or Child class B or C cirrhosis (Figure 6).[5] For patients not receiving prophylaxis with a nonselective beta-blocker, EGD should be repeated in 2 years, or at the time of hepatic decompensation, or annually for those with decompensated liver disease. Patients already taking a nonselective beta-blocker do not need a follow-up EGD.

Large Esophageal Varices

In patients with large varices (diameter greater than 5 mm) (Figure 7) that have not bled, both nonselective beta-blockers and endoscopic variceal ligation lower the incidence of first variceal hemorrhage. In a meta-analysis, endoscopic variceal ligation reduced risk of bleeding slightly more than nonselective beta-blocker use, but there was no difference in mortality and endoscopic variceal ligation is associated with a risk of procedure-related complications.[6]

Recommended Prophylaxis against Variceal Hemorrhage

Primary prophylaxis is recommended for patients with large varices, and for those with small varices who also have red wale marks on varices or Child class B or C cirrhosis. Primary prophylaxis against variceal hemorrhage includes pharmacologic therapy with nonselective beta-blockers and endoscopic variceal ligation for patients with large varices who are unable to receive nonselective beta-blockers (Figure 8). The nonselective beta-blockers decrease cardiac output (beta-1 effect) and induce splanchnic vasoconstriction (beta-2 effect), which decreases venous portal blood inflow. In most of the published studies, investigators titrated the nonselective beta-blockers to decrease the heart rate by 25% from baseline, but since the heart rate reduction does not correlate with HVPG reduction, most experts recommend increasing to the maximally tolerated dose, or until the heart rate is approximately 55 beats per minute. There is promising data on carvedilol as a possible well-tolerated alternative agent.[7,8] Patients receiving variceal prophylaxis need to continue the
nonselective beta-blocker indefinitely, but they do not need follow-up EGD. For those patients with large varices who have a contraindication to or intolerance of nonselective beta-blockers, endoscopic variceal ligation should be performed every 2 to 4 weeks until the varices are eradicated. After obliteration is achieved, patients will need to continue with surveillance EGDs every 6 to 12 months indefinitely.
Treatment of Acute Variceal Bleeding

Variceal bleeding accounts for 70% of all cases of upper gastrointestinal bleeding in patients with cirrhosis. Esophageal variceal bleeding spontaneously resolves in 40 to 50% of cases, but there is a 30 to 40% chance of early rebleeding in the first 6 weeks. Initial treatment of bleeding is effective in 80 to 90% of cases but mortality remains approximately 15 to 20%, with the majority of deaths due to liver failure, hepatorenal syndrome, and infections, and occurring predominantly in Child class C cirrhotic patients. The management of variceal bleeding requires a multi-pronged approach (Figure 9).[3]

General Management

Patients with suspected variceal hemorrhage should be admitted to the intensive care unit. Establishing intravenous access and providing volume resuscitation should be performed immediately to achieve hemodynamic stability. Blood transfusion should be restricted to a hemoglobin level of 7 g/dL or lower, as excessive transfusion increases portal pressure, risk of rebleeding, and mortality.[9]

Pharmacologic Therapy

A vasoconstrictor agent should be started at the time of admission and continued for 2 to 5 days. Terlipressin, a synthetic vasopressin analogue, has been shown to decrease mortality but is not widely available in the United States. Instead, octreotide (Sandostatin), a somatostatin analogue, is available in the United States.[10] Its efficacy is controversial as it is associated with tachyphylaxis, but it may provide some benefit when used in combination with endoscopic therapy.[11, 12]

Endoscopic Therapy

Endoscopic therapy, preferably endoscopic variceal ligation, should be performed within 12 hours of admission. Sclerotherapy is an option when endoscopic variceal ligation is not technically feasible.

Infection Prophylaxis

The use of prophylactic antibiotics (norfloxacin or ceftriaxone) decreases the rate of bacterial infection, risk of early rebleeding, and mortality.[13]

Rescue Therapy

Rescue therapy is still warranted in 10 to 20% of cases due to failure to control bleeding or recurrent bleeding. Early placement of a transjugular intrahepatic portosystemic shunt (TIPS) within 24 to 48 hours after admission has been shown to improve survival in patients at high risk of rebleeding (HVPG greater than or equal to 20 mm Hg or Child class C cirrhosis).[14, 15] Balloon tamponade can assist with temporary control of hemorrhage in patients with difficult to control bleeding awaiting more definitive therapy (e.g. TIPS or endoscopic therapy).

Gastric Varices

Gastric varices are present in 20% of patients with portal hypertension, but only account for 5 to 10% of all cases of upper gastrointestinal bleeding in cirrhotic patients. Acute fundal gastric variceal bleeding (1 to 3% of all variceal bleeding episodes) is associated with a higher rate of death than gastroesophageal varices as the bleeding is usually more severe.[16] Endoscopic variceal obturation with tissue adhesive (e.g. N-butyl-2-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin) is preferred over endoscopic variceal ligation for initial management of bleeding.[17, 18] This technique
requires special endoscopic expertise, so if it is not available, TIPS can also be used to control the bleeding successfully as first-line therapy or in cases of recurrent bleeding.[19]
Secondary Prophylaxis of Variceal Bleeding

Untreated cirrhotic patients with a history of variceal bleeding have a 60% risk of rebleeding within 1 to 2 years, with a 20% risk of dying with each episode. In the absence of TIPS, patients should be started on prophylactic therapy with a nonselective beta-blocker prior to discharge from the hospital.

Pharmacologic Therapy

Nonselective beta-blockers reduce the variceal rebleeding rate to around 43%. The combination of a nonselective beta-blocker and isosorbide mononitrate may lower the bleeding rate further, but this combination has greater side effects and is poorly tolerated. Thus, most patients use nonselective beta-blockers alone.

Endoscopic Therapy

Endoscopic variceal ligation therapy is superior to sclerotherapy for secondary prophylaxis and decreases the rebleeding rate to around 32%. Sessions are repeated every 7 to 14 days until the varices are gone and then are repeated every 3 to 6 months for surveillance.

Combination Therapy

The combination of pharmacological and endoscopic therapy is superior over either modality alone in decreasing the rebleeding rate to 14 to 23%, although there is no statistical difference in mortality.[20]

Portosystemic Shunt

Placement of a transjugular intrahepatic portosystemic shunt is very effective in preventing rebleeding but has no impact on survival and is associated with an increased risk of hepatic encephalopathy. Similarly, transjugular intrahepatic portosystemic shunt has been shown to be superior to endoscopic therapy and pharmacologic therapy in reducing the risk of rebleeding but with no difference in mortality, an increased risk of hepatic encephalopathy, and increased costs. In general, placement of transjugular intrahepatic portosystemic shunt should be reserved for Child's class A and B cirrhotic patients who fail the combination of pharmacologic and endoscopic therapy.

Referral for Liver Transplantation Evaluation

Patients who are otherwise liver transplantation candidates should be referred to a transplant center for consideration of an evaluation.
Summary Points

- Portal hypertension results from increased resistance to portal flow (fixed and dynamic) and increased portal venous blood inflow (splanchnic vasodilatation and increased cardiac output).
- All cirrhotic patients should undergo EGD for variceal screening at the time of diagnosis, unless they are already using a nonselective beta-blocker. If no varices are found, the EGD examination should be repeated in 2 to 3 years or at the time of hepatic decompensation.
- Small esophageal varices (in the absence of red wale marks or Child's class B or C cirrhosis) do not warrant prophylaxis but repeat EGD should be done in 2 years or at time of hepatic decompensation and yearly thereafter once decompensation occurs.
- The nonselective beta-blockers are recommended for the prevention of the first variceal hemorrhage in those with large esophageal varices or small esophageal varices at high risk of bleeding (red wale marks or Child class B or C cirrhosis). If nonselective beta-blockers are contraindicated or not tolerated, EVL can be performed.
- Acute variceal hemorrhage is managed with the combination of a vasoconstrictor agent, such as octreotide, and EVL. Transjugular intrahepatic portosystemic shunt is reserved as rescue therapy and may be considered earlier in patients at high risk for rebleeding (e.g. HVPG greater than or equal to 20 mmHg or Child class C cirrhosis.) Use of prophylactic antibiotics during acute variceal bleeding reduces the risk of rebleeding and mortality.
- Bleeding gastric varices can be treated using endoscopic variceal obturation using tissue adhesives or a transjugular intrahepatic portosystemic shunt.
- In patients who have previously bled, the combination of nonselective beta-blockers and EVL reduces the risk of rebleeding. A transjugular intrahepatic portosystemic shunt procedure decreases the risk of rebleeding further but does not impact survival, so it is reserved for those who fail combination pharmacologic and endoscopic therapy.
Citations

   [PubMed Abstract]

   [PubMed Abstract]

   [AASLD Practice Guidelines]

   [PubMed Abstract]

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   [PubMed Abstract]

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    [PubMed Abstract]

    [PubMed Abstract]


References


Figures

Figure 1 Prognostic Value of Hepatic Venous Pressure Gradient (HVPG) in Patients with Chronic Liver Disease


<table>
<thead>
<tr>
<th>Measurement</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 mm Hg</td>
<td>Normal</td>
</tr>
<tr>
<td>6-10 mm Hg</td>
<td>Preclinical sinusoidal portal hypertension</td>
</tr>
<tr>
<td>≥ 10 mm Hg</td>
<td>Clinically significant portal hypertension</td>
</tr>
<tr>
<td>≥ 12 mm Hg</td>
<td>Increased risk for rupture of varices</td>
</tr>
<tr>
<td>≥ 16 mm Hg</td>
<td>Increased risk of mortality</td>
</tr>
<tr>
<td>≥ 20 mm Hg</td>
<td>Treatment failure and mortality in acute variceal bleeding</td>
</tr>
</tbody>
</table>
Figure 2 Cirrhotic Liver without Esophageal Varices

The left side of the illustration shows a patient with moderately advanced cirrhosis. The inset shows an internal longitudinal view of the esophagus, with absence of esophageal varices. The far right inset shows the esophageal view as seen from the operator of the endoscope.

Illustration by David W. Ehlert, CMI, MAMS. Cognition Studio
Figure 3 Cirrhotic Liver with Esophageal Varices

The left side of the illustration shows a patient with advanced cirrhosis and marked dilatation of surrounding veins. The inset shows an internal longitudinal view of the esophagus, with the presence of esophageal varices. The far right inset shows the esophageal view of the visible varices as seen from the operator of the endoscope.

Illustration by David W. Ehlert, CMI, MAMS. Cognition Studio
Figure 4 Endoscopic View of Small Esophageal Varices

Endoscopic view of the esophagus, looking down into the esophageal lumen. The white arrows indicate the presence of small esophageal varices.

Photograph courtesy of Dr. Iris Liou, University of Washington.
Figure 5 Endoscopic View Red Wale Markings on Esophagus

Endoscopic view of the esophagus, looking down into the esophageal lumen. The black arrows indicate the presence of red wale markings (red marks or red spots) on esophageal varices.

Photograph courtesy of Dr. Iris Liou, University of Washington.
**Figure 6 Child-Turcotte-Pugh Classification**

The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.


<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points†</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)*

**Class A** = 5 to 6 points (least severe liver disease)

**Class B** = 7 to 9 points (moderately severe liver disease)

**Class C** = 10 to 15 points (most severe liver disease)
Figure 7 Endoscopic View of Large Esophageal Varices

Endoscopic view of the esophagus, looking down into the esophageal lumen. The white arrows indicate the presence of two columns of large esophageal varices.

Photograph courtesy of Dr. Iris Liou, University of Washington.
**Figure 8 Primary Prophylaxis against Variceal Hemorrhage**

All medications listed are oral regimens.


<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose and Frequency</th>
<th>Goal</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>6.25 mg once a day</td>
<td>Maximal tolerance or heart rate 55 beats per minute, up to a dose of 12.5 mg once a day</td>
<td>Assess heart rate at every visit</td>
</tr>
<tr>
<td>Nadolol</td>
<td>20 to 40 mg once a day (adjust for renal insufficiency)</td>
<td>Maximal tolerance or heart rate 55 beats per minute</td>
<td>Assess heart rate at every visit</td>
</tr>
<tr>
<td>Propanolol</td>
<td>20 mg twice a day</td>
<td>Maximal tolerance or heart rate 55 beats per minute</td>
<td>Assess heart rate at every visit</td>
</tr>
<tr>
<td>Endoscopic variceal ligation</td>
<td>Every 2 to 4 weeks</td>
<td>Variceal obliteration</td>
<td>Surveillance EGD 1 to 3 months after initial obliteration, then once every 6 to 12 months</td>
</tr>
</tbody>
</table>

EGD = esophagogastroduodenoscopy
## Figure 9 Treatment of Acute Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Management</strong></td>
<td>Admit to intensive care unit</td>
</tr>
<tr>
<td></td>
<td>Resuscitation but limit transfusion to hemoglobin level of 7 g/dL</td>
</tr>
<tr>
<td></td>
<td>Secure intravenous access</td>
</tr>
<tr>
<td></td>
<td>Consider intubation and mechanical ventilation</td>
</tr>
<tr>
<td><strong>Vasoconstrictor</strong></td>
<td>IV octreotide (50 μg bolus then 50 μg/hour infusion x 2 to 5 days)</td>
</tr>
<tr>
<td></td>
<td>IV terlipressin (2 mg every 4 hours for first 48 hours, followed by 1 mg</td>
</tr>
<tr>
<td></td>
<td>every 4 hours x 2 to 5 days)</td>
</tr>
<tr>
<td><strong>Antibiotic Prophylaxis</strong></td>
<td>IV ceftriaxone 1 gm daily x 7 days (preferred in Child class B and C)</td>
</tr>
<tr>
<td></td>
<td>Oral norfloxacin 400 mg twice a day x 7 days</td>
</tr>
<tr>
<td><strong>Endoscopic Therapy</strong></td>
<td>Endoscopic variceal ligation (preferred)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic variceal sclerotherapy</td>
</tr>
<tr>
<td><strong>Salvage Therapy</strong></td>
<td>Balloon tamponade (only temporary, maximum 24 hours)</td>
</tr>
<tr>
<td></td>
<td>Transjugular intrahepatic portosystemic shunt</td>
</tr>
</tbody>
</table>