Portal hypertension is defined as an increase in portal venous pressure more than 5 mm Hg. Clinically, portal hypertension manifests as overt haematemesis and/or splenomegaly. Endoscopically, it is recognized by the presence of varices (esophageal and gastric).

Classification of Esophageal varices

\( F_1 \) - Small straight varices

\( F_2 \) - Enlarged, tortuous, occupy less than one-third of lumen.

\( F_3 \) - Large, coil shaped, occupy more than one-third of lumen.

Classification of Gastric Varices (Baveno Consensus Conference)

A. Gastroesophageal Varices
   - Type I (GEV 1) – along the lesser curve
   - Type II (GEV 2) – along the greater curve extending toward the gastric fundus.

B. Isolated Gastric Varices
   - Type I (IGV 1) – isolated cluster of varices in the gastric fundus.
   - Type II (IGV 2) – isolated gastric varices in the other parts of the stomach.

Definitions in Context of a Variceal Bleed

Variceal hemorrhage: is defined as bleeding from an esophageal or gastric varix at the time of endoscopy or the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding.

Clinically significant variceal bleeding – If two or more units of blood are required within first 24 hours of admission along with a systolic blood pressure of less than 100 mm Hg or a postural change of greater than 20 mm Hg and/or pulse rate greater than 100 beats/min.

Variceal rebleeding: is defined as occurrence of new haematemesis or malena more than 24 hr after the patient has had stable vital signs and haemoglobin/haematocrit following an index bleed.
Natural History of Varices in Cirrhosis

Incidence of varices among cirrhosis is approximately 50%. Cirrhotics develop varices at the rate of 5-15% per year. About one-third of patients with varices experience variceal blood. The most important factor in development of varices is degree of portal hypertension. A useful clinical marker of portal hypertension is the hepatic venous pressure gradient (HVPG). It is defined as the gradient between the wedged hepatic venous pressure and the free hepatic venous pressure (normal HVPG <5 mm Hg). Reducing HVPG below 12 mm Hg or by at least 20% is associated with significant protection against bleeding. This pressure has been accepted as the aim of pharmacotherapy. Gastric varices bleed less frequently but more severely than esophageal varices.

The risk factors for first variceal bleed are pressure within the varix, variceal size, tension on the variceal wall and severity of the liver disease. Rebleeding is associated with severity of liver failure, ascites, active alcoholism and red signs on varices. Red sign represent a small area of a varix with a very thin and weak wall, usually resulting from maximum distension of vessel. A new noninvasive method of measuring intravariceal pressure has been introduced. The device is constructed by placing a 20 MHz ultrasound transducer in a latex balloon catheter attached to as pressure transducer.

Management of Active Variceal Bleed

The management options for control of active variceal bleeding and its prevention include pharmacological agents, endoscopic interventions, balloon tamponade, surgical management and radiological interventions (Table 1).

Endoscopic therapy has been the primary treatment modality in acute variceal hemorrhage. Traditionally, endoscopic sclerotherapy (EST); and recently, endoscopic variceal ligation (EVL) are used for control of acute esophageal variceal bleed. Their wide availability, relative ease of learning, safety and potential of instituting this therapy at the time of diagnosis are few of the advantages. Gastric varices in continuity with esophageal varices along the lesser curvature may also respond, while high fundal varices respond poorly.

Endoscopic Sclerotherapy

The frequently used sclerosants in EST are sodium morrhuate, ethanolamine oleate, sodium tetradecyl and absolute alcohol. Comparative studies have not shown any individual sclerosant or combination to be superior to any other. During an acute bleed, the injections are usually intravariceal while in elective situations, paravariceal sclerotherapy is also equally effective. Varices are injected beginning at the gastroesophageal junction. Each injection consists of 1 to 2 ml to a total of 20 ml per session. Repeat EST is performed within a week, then at about 3 week intervals. After obliteration, varices tend to recur over time in 50 to 70% of individuals. Hence surveillance endoscopy must be performed at 6 month interval for one year and annually thereafter.

Endoscopic Variceal Ligation

An elastic band is used to strangulate superficial blood vessel, resulting in vessel thrombosis and mural scar formation up to, but not including, the muscularis propria. The endoscope is advanced to the distal esophagus, a varix is suctioned into the banding device, and a band is released by the trigger wire. The bands are deployed circumferentially in the distal esophagus in a manner similar to that for EST. EVL is associated with superficial mucosal ulcers (90% at one week) but development of dysphagia from strictures and systemic complications are rare.

N-butyl-2-cyanoacrylate injection is considered to be the treatment of choice for bleeding fundal varices. The distinct decline in the rebleeding rates during the follow up is result of complete variceal eradication or obliteration achieved by repeated injection therapy.
Non Surgical Treatment of Portal Hypertension

2-Octyl-Cyanoacrylate (Dermabond), an FDA approved agent for superficial wound closure, has been shown to be effective in controlling variceal bleed in initial studies in animal models. If Dermabond is used in humans, a higher volume of injection relative to that with N-butyl-2-cyanoacrylate would be needed.

Human Fibrin glue (Beriplast-P) consists of a mixture of human fibrinogen, factor III and human thrombin. It achieved immediate hemostasis with a single injection in 70% of the patients in an open pilot study. In the remaining patients, significant bleeding occurred immediately on withdrawal of the injection needle from the varix, due to the relatively large size of the injection needle. Hence, larger trials are needed to substantiate its use in patients.

EVL with Argon Plasma Coagulation (APC)
To improve the rate of long-term eradication of esophageal varices following EVL, APC and low power diode laser treatment have been recommended. The idea behind additional use of APC is to promote fibrosis of the esophageal inner wall. The cumulative recurrence free rate was significantly higher in the combined group (EVL + APC) as compared to EVL alone. However higher incidence of pyrexia was noted.

---

Table 1: Recommendations for control of Active Variceal Bleeding

Ideally patients with variceal bleeding should be treated in a unit where the personnel are familiar with the management of such patients and where routine therapeutic interventions can be undertaken.

1. **Resuscitation**
   - **Site:** Where haemodynamic monitoring is possible.
   - **Methods:**
     - 16 gauge peripheral cannulas, at least 2.
     - Cross match 6 units of blood.
     - Correct prothrombin time, platelet count.
     - Central venous access.
     - Protection of the airway by elective intubation:
       - (i) severe uncontrolled variceal bleeding
       - (ii) severe encephalopathy;
       - (iii) inability to maintain oxygen saturation above 90%;
       - (iv) aspiration pneumonia.

2. **TIMING OF UPPER GASTROINTESTINAL ENDOSCOPY**
   - As soon as the patient is haemodynamically stable.

3. **CONTROL OF BLEEDING**
   - Variceal band ligation is the method of first choice.
   - If banding is difficult because of continued bleeding or this technique is not available, endoscopic variceal sclerotherapy should be performed.
   - If endoscopy is unavailable. Vasoconstrictors such as octreotide or terlipressin, or a Sengstaken tube (with adequate provision for airways protection) may be used while more definitive therapy is arranged.

4. **FAILURE TO CONTROL ACTIVE BLEEDING**
   - In case of bleeding that is difficult to control, a Sengstaken tube should be inserted until further endoscopic treatment. TIPS, or surgical treatment.
   - Specialist help should be sought at this time and transfer to a specialist centre should be considered.
   - The mode of treatment- that is, surgical intervention such as esophageal transaction or TIPS is decided by which of these techniques is routinely used by the centre in which this patient is being managed.
Pharmacological Therapy (Table 2)
Pharmacological therapy is used in situations where endoscopy is unavailable.

Vasopressin and Its Analogues
A combination of vasopressin and nitroglycerin are used in an attempt to reduce side effects of vasopressin. Various trials have shown that it improves control of bleeding but without an effect on mortality. Terlipressin, synthetic vasopressin analogue with longer half life, has been shown to be better than placebo and similar in efficacy to balloon tamponade. It is the only pharmacological agent that has been reported to improve survival in patients with active variceal haemorrhage.

Somatostatin and Its Analogues
Somatostatin has been shown to be superior to vasopressin and balloon tamponade. However, octreotide (long acting analogue of somatostatin) has been shown to be equivalent to sclerotherapy and to improve the outcome of subjects who received the drug along with endoscopic treatment, when compared with those receiving EST or EVL alone.

Balloon Tamponade
This form of treatment is highly effective and controls acute bleeding in upto 90% of patients although about 50% rebleed when the balloon is deflated. It is associated with serious complications such as oesophageal ulceration and aspiration pneumonia in 15-20% patients. Despite this, it may be life-saving.

<table>
<thead>
<tr>
<th>Table 2: Pharmacologic Agents used in Portal Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>∏-adrenergic antagonists</td>
</tr>
<tr>
<td>Nonselective : propranolol, nadolol, carvedilol</td>
</tr>
<tr>
<td>Selective : β1-and β2-adrenergic antagonists</td>
</tr>
<tr>
<td>Vasopressin and its analogues</td>
</tr>
<tr>
<td>Vasopressin (0.1 to 0.4 U/min)</td>
</tr>
<tr>
<td>Terlipressin</td>
</tr>
<tr>
<td>Omnipressin</td>
</tr>
<tr>
<td>Somatostatin and its analogues</td>
</tr>
<tr>
<td>Somatostatin ( initial 250µg bolus, constant infusion of 250µg/h)</td>
</tr>
<tr>
<td>Octreotide (50-100 µg/h)</td>
</tr>
<tr>
<td>Nitrovasodilators</td>
</tr>
<tr>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
</tr>
<tr>
<td>Isosorbide 5-mononitrate</td>
</tr>
<tr>
<td>Centrally acting α-adrenergic agonists*</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Diuretics*</td>
</tr>
<tr>
<td>Loop diuretics: furosemide, bumetanide</td>
</tr>
<tr>
<td>Distal diuretics: spironolactone, amiloride</td>
</tr>
<tr>
<td>Miscellaneous agents*</td>
</tr>
<tr>
<td>Calcium channel blockers : verapamil</td>
</tr>
<tr>
<td>α-adrenergic agonists : prazocin</td>
</tr>
</tbody>
</table>

* Data on clinical efficacy is limited.
saving treatment in massive uncontrolled variceal hemorrhage pending other forms of treatment.

Transjugular Intrahepatic Portosystemic Shunts (TIPS)
Studies have specifically addressed the role of TIPS in the management of uncontrolled variceal haemorrhage. They show that TIPS can be performed successfully in this situation and is associated with rapid control of bleeding. TIPS offers the best salvage therapy in patients with failed hemostasis or breakthrough recurrent bleeding despite medical and endoscopic therapy.

Liver Transplantation
This is probably only appropriate for patients who bleed while awaiting liver transplantation although studies using EVL or comparison with TIPS in this situation need to be done. No controlled trial of liver transplantation in uncontrolled/active bleeding is available.

Primary Prophylaxis (Table 3)
About 30-50% patients with portal hypertension will bleed from varices. β blockers reduce the incidence of initial variceal hemorrhage by approximately 45% and decrease bleeding related mortality by 50%. This beneficial effect was noted only in those who had HVPG less than 12 mm Hg or had a 20% or more reduction in HVPG. Sudden treatment cessation is associated with an increased risk of rebound hemorrhage and should be avoided.

EST is not recommended for the primary prophylaxis of variceal hemorrhage. EVL appears to eradicate esophageal varices with fewer complications than EST. Several reports show that EVL was superior to either no therapy or β-blockers with respect to prevention of index bleeding as well as survival. Until corroborated by bigger studies, EVL cannot be recommended for routine clinical use for primary prophylaxis of variceal hemorrhage.

Secondary Prophylaxis
This form of treatment is aimed at preventing recurrence of variceal bleeding (Table IV).

Table 3 : Primary Prophylaxis of Variceal Bleeding in cirrhosis

What is the Best Method for Primary Prophylaxis?
- Pharmacological therapy with propranolol is the best available modality at present.
- Aim of therapy with propranolol: Reduction in hepatic venous pressure gradient to less than 12 mm Hg.
- Dose: Starting dose 40 mg twice daily, increasing to 80 mg twice daily if necessary. Long acting propranolol at either 80 or 160 mg can be used to improve compliance.
- In case of contraindications or intolerance to propranolol, variceal band ligation is the treatment of choice.
- In difficult situations where neither propranolol nor variceal band ligation can be used, isosorbide mononitrate is the treatment of first choice (20 mg twice daily).

Who Should Have Surveillance for Variceal Bleeding?
- All patients with cirrhosis should be endoscoped at the time of diagnosis.

How Often Should Cirrhotic Patients be Endoscoped?
- If at the time of first endoscopy no varices are observed, patients with cirrhosis should be endoscoped at three year intervals.
- If small varices are diagnosed, patients should be endoscoped at yearly intervals.

Which Patients with Cirrhosis Should have Primary Prophylaxis?
- If grade 3 varices are diagnosed, patients should have primary prophylaxis irrespective of the severity of the liver disease.
- If patients have grade 2 varices and Child class B or C disease, they should have primary prophylaxis.
EVL is known to be superior to EST in terms of initial eradication, rebleeding, morbidity and mortality. However EVL is associated with a high rate of variceal recurrence and its efficacy is significantly lower in patients with Child-Pugh grade C cirrhosis. TIPS reduces rebleeding and is associated with an increased risk of encephalopathy. No differences in survival were observed between patients treated with TIPS or endoscopic therapy. Despite the problem of shunt insufficiency and the cost of shunt surveillance, TIPS has been shown to be more cost effective than endoscopic therapy.

Studies on pharmacotherapy of secondary prophylaxis have focused on beta-blockers, long acting nitrates and combined drug therapy. Various trials have concluded that beta-blockers (propranol, nadolol, atenolol) significantly reduce the risk of variceal rebleeding. Beta-blockers have the additional benefit of reducing the risk of bleeding from portal hypertensive gastropathy. Nitrates are generally used in secondary prophylaxis, if beta-blockers are contraindicated or not tolerated. Several other drugs (clonidine, diuretics, verapamil, metoclopramide) also have been studied, but their efficacy in the clinical setting is unproven or their use is still confined to experimental studies.

**Antibiotics in Variceal Bleeding**

Bacterial infections occur in about 20% of patients with upper gastrointestinal bleeding within 48 hours of admission and the incidence increases to 35-66% within two weeks. Prognosis both in terms of rebleeding, failure to control bleeding, and in hospital outcome are closely related to bacterial infections. Antibiotic prophylaxis is associated with significantly improved short term survival. It is suggested that patients with cirrhosis and upper gastrointestinal bleeding should have antibiotic prophylaxis. Fluoroquinolone (Ciprofloxacin) is the simplest measure, at a dose of 1 gm per day orally and may be the antibiotic of choice.

**References**