

PSG PRACTICE GUIDELINES ON THE MANAGEMENT OF VARICEAL BLEEDING, PESHAWAR, PAKISTAN 2006

Javed Iqbal Farooqi^{*,¶}

Chairman PSG Consensus Meeting, Peshawar, Pakistan 2006

* Tel: + 0092-333-9123818;

E-mail address: dr_farooqi@hotmail.com

¶ On behalf of Chairpersons, Moderators and Panelists of PSG Consensus Meeting, Peshawar, Pakistan 2006

The following chaired sessions during the Meeting:

Jan Muhammad Memon, SM Wasim Jafri, Najib-ul-Haq, Muhammad Sadiq Shah, Nasratullah Chaudhary, Muhammad Umar

The following moderated working committees during the Meeting:

Arif Amir Nawaz, Shakeel Ahmed Mirza, Khalid Hameed

The following participated in the presentations and discussions as Panelists:

Saad Khalid Niaz, Saeed S Hamid, Muhammad Umar, Zaigham Abbas, Syed Hasnain Ali Shah, Ghias-un-Nabi Tayyab, Nasir Khokhar, Badar Fayyaz Zuberi, Muhammad Saeed Qureshi, Tassawar Hussain, Zafar Hayat, Syed Musanif Shah, Massod Siddiq, SM Qamarularfin, Masood-ur-Rehman, Javed Aslam Butt, Bushra Khaar, Muhammad Shoaib Shafi, Syed Pervaiz Asghar, Farooq Khattak, Hamayun Zafar, Rukhsana Javed Farooqi, Ijaz Muhammad Khan, Riaz Hussain Shah, Aamir Ghafoor, Bakhth Biland, Habib Jadoon, Noor Muhammad, Hameed Ahmed, Faiz-ur-Rehman, Farooq Ahmed, Mumtaz Marwat, Sher Rehman, Abbas Khattak, Jamal Din, Aziz Ahmed, Khalid Mehmood.

The following gave review lectures during the Meeting:

Muhammad Umar, Zaigham Abbas, Syed Hasnain Ali Shah, Ghias-un-Nabi Tayyab, Nasir Khokhar, Badar Fayyaz Zuberi, Muhammad Saeed Qureshi

The following reviewed the consensus statement document:

Saeed S Hamid, Zaigham Abbas, Nasir Khokhar, Arif Amir Nawaz, Saad Khalid Niaz, Muhammad Umar, Shakeel Ahmed Mirza, Syed Hasnain Ali Shah, Ghias-un-Nabi Tayyab, Badar Fayyaz Zuberi, Muhammad Saeed Qureshi, Bushra Khaar, Muhammad Shoaib Shafi, Hamayun Zafar, Rukhsana Javed Farooqi.

Gastroesophageal variceal bleeding is a major complication of portal hypertension resulting from cirrhosis. It occurs in 25 to 35 percent of patients with cirrhosis and accounts for 80 to 90 percent bleeding episodes in these patients.¹⁻³ Variceal bleeding is associated with more substantial morbidity and mortality than other causes of gastrointestinal bleeding, as well as higher economical burden.⁴⁻⁶ Up to 30 percent of initial bleeding episodes are fatal and as many as 70 percent of survivors have recurrent bleeding within one year.^{1,7} Therefore, one-year survival rate after variceal bleeding is poor ranging from 32 to 80 percent.^{7,8} Over the past few years, there have been numerous advances in the management of variceal bleeding in patients with cirrhosis. These include better endoscopic techniques, establishment of variceal ligation, drugs like Terlipressin and Octreotide, better surgical techniques, and finally the availability of TIPSS. During last few years, many milestones review articles and guidelines including UK guidelines,⁹ OMGE guidelines,¹⁰ Baveno IV workshop,¹¹ etc., have been published to suggest the evidence based appropriate management of patients with variceal bleeding.

Pakistan has some unique factors: (1) Prevalence of Hepatitis and Liver Cirrhosis and its associated complications is still on rise, (2) Access to health care is only patchy and very limited, (3) There is lack of adequate diagnostic facilities including endoscopic equipment, cost of accessories and maintenance costs are extremely high, (3) Training slots are deficient for healthcare workers, (4) Patient attitudes towards specialized care is another hurdle in delivering the best treatment, (5) Lack of affordability on patients part, (6) Lack of more definitive therapies for cirrhotic patients including Liver Transplant and TIPS. Therefore **Pakistan Society of Gastroenterology & GI Endoscopy** decided to hold **National Consensus Meeting** to develop National Practice Guidelines for the Management of Variceal Bleeding in our country taking into consideration our resources and poor but multifaceted healthcare system. **PSG National Consensus Meeting** was held on January 7–8, 2006 in **Peshawar**. The meeting was attended by experts from all over the country. Three committees were made in advance including i) to review literature and make guidelines on the management of acute variceal bleeding, ii) to review literature and make guidelines on the primary prophylaxis of variceal bleeding, and iii) to review literature and make guidelines on the secondary prophylaxis of variceal

bleeding. All the relevant world and local literature including review articles, guidelines statements, original research data, were sent in advance to more than 100 experts of the country along with the questionnaire. Meeting comprised the followings:

- **Part I:** Seven Review-Lectures along with two sessions of panel discussions
- **Part II:** separate meetings of the three committees to propose guidelines
- **Part III:** Joint meeting to review and approve the proposed guidelines

During the meeting, a series of consensus statements, review articles and available data were discussed and agreed upon. The available evidence was graded^{12,13} according to the criteria given in Table – 1. All recommendations for clinical practice were graded^{9,14-16} according to the criteria given in table – 2.

These **National Practice Guidelines** are officially approved by **Pakistan Society of Gastroenterology & GI Endoscopy** and provide a data-supported approach towards management of variceal bleeding in Pakistan. These are preferred approaches to the diagnostic, therapeutic and preventive aspects of care. These are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case.

PATHOGENESIS OF PORTAL HYPERTENSION

Although the pathogenesis of portal hypertension is complex, and a detailed discussion of this topic is beyond the scope of this consensus statement; in brief, it can be easily understood by Ohm's Law which states that pressure along a vessel (P) is directly related to flow in the vessel (Q) and resistance to the flow (R), as shown below:

$$P = Q \times R$$

In cirrhosis liver, both the blood flow (Q) and resistance through the liver (R) are increased resulting in portal hypertension, as discussed below:

- **Hyperdynamic splanchnic circulation:** Studies¹⁷⁻¹⁹ suggest an imbalance between the potent vasoconstrictor *endothelin-1* and the potent vasodilator *nitric-oxide* which leads to net vasodilatation in the splanchnic and systemic circulation. As a consequence, the adrenergic (increased cardiac output) and the rennin-angiotensin systems (renal Na⁺ and water retention) are activated as counter-regulatory

mechanisms, resulting in the hyperdynamic circulation typically associated with cirrhosis.

- **Increased intrahepatic resistance:** There is deranged hepatic (vascular) architecture in cirrhosis liver which increases intrahepatic resistance to portal blood flow.

DEVELOPMENT OF VARICES

Varices are portosystemic collaterals which are formed when portal hypertension dilates the preexisting vascular channels: (a) at the cardia through the intrinsic and extrinsic gastroesophageal veins, (b) in the anal canal where superior haemorrhoidal vein anastomoses with middle & inferior haemorrhoidal veins, (c) in the falciform ligament of liver through paraumbilical veins, (d) in the abdominal wall and the retroperitoneal tissues veins in the lineorenal ligament, in the omentum and lumbar veins, and (e) blood diversion from the diaphragm, gastric, pancreatic, splenic, and adrenal which may drain into the left renal vein. The distal 2 to 5 cm of the esophagus – the most common site of varices – contains superficial veins that lack support from surrounding tissues,²⁰ a feature consistent with the occurrence of prominent bleeding at this site. The dilatation of distal esophageal varices depends on a threshold pressure gradient. Hepatic Venous Pressure Gradient (HVPG) is the most commonly used measured pressure. It is defined as the gradient between the wedged (occluded) hepatic venous pressure and the free hepatic venous pressure. It indicates the pressure difference between portal and systemic circulation. Normal gradient is < 5 mm Hg. Varices form when HVPG is at least 12 mm Hg^{21,22} or more²³ – this pressure is necessary, but not sufficient for all varices to form.

NATURAL HISTORY OF VARICES

Studies suggest that varices develop and enlarge with time if untreated. Approximately 30% of cirrhotics have varices at the time of diagnosis; this proportion increases with time and reaches 90% after approximately 10 years.²⁴⁻²⁶ The average lifetime risk of variceal bleeding for those patients with cirrhosis who have not previously bled is around 30%.²⁷ The incidence of first bleeding episode varies from 12% to 30% at 1 year and from 5% to 61% at 2 years.^{1,28} The risk of bleeding is highest within the first year of diagnosis.²⁹

PATHOGENESIS OF VARICEAL BLEEDING

Despite the high prevalence of varices in patients with cirrhosis, bleeding only occurs in about one third of patients.^{1,2} The pathogenesis of variceal rupture can be easily understood by Frank's modification of Laplace's Law²⁰ which states that *variceal wall Tension (T)* is proportionate to the Transluminal Pressure (TP), the radius of the varix (r), and the thickness of the variceal wall (w), as shown below:

$$T = [TP \times r] \times w^{-1}$$

Where Transluminal Pressure (TP) is the gradient between intraluminal variceal pressure (TP₁) and esophageal luminal pressure (TP₂) [TP = TP₁ – TP₂].

Variceal wall Tension (T) is a property of the variceal wall which can be thought of as an inwardly directed force which opposes an expanding force which, in turn, is proportional tontransluminal pressure and radius and inversely proportional to wall thickness. As the varix distends, *variceal wall Tension (T)* i.e. resistance to further distension, also increases. At high levels of distension, the elastic limit of the variceal wall is approached and small increments of increase in TP or variceal radius are associated large changes in *variceal wall tension (T)*. When the elastic limit of the varix is reached, further distension cannot be counteracted by further increase in *wall Tension (T)*. At this point, variceal rupture ruptures.

In most cases, portal pressure reflects intravariceal pressure³⁰ and a HVPG greater than 12 mm Hg is necessary for the development of and bleeding from varices but there is no linear relationship between the severity of portal hypertension and the risk of bleeding.^{21,23} However, the HVPG tends to be higher in bleeders as well as in patients with larger varices. Varices do not bleed, if HVPG is below 12 mmHg.²

PREDICTION OF VARICEAL BLEEDING

For optimal management, it is important to understand which patients are most likely to bleed. Following are the factors which can predict variceal bleeding:

- **Clinical Factors** include continued alcohol use and poor liver function¹
- **Endoscopic Predictors** include large varices and endoscopic red signs (e.g., red wale markings) on the variceal wall^{1, 31}

A combination of these clinical and endoscopic findings including advanced Child-Pugh class of cirrhosis³² (Table-3) correlate highly with the risk of a first bleeding episode in patients with cirrhosis¹. Hemodynamic measurement such as the HVPG, the intravariceal pressure, and the Doppler ultrasonographic measurement of portal pressure have been used in efforts to predict variceal bleeding. The HVPG provides a reliable measure of portal pressure in most patients with cirrhosis (but can underestimate portal pressure in patients with presinusoidal portal hypertension).³³ Furthermore, an increasing HVPG predicts an increased risk of bleeding, and the extent of the elevation of portal pressure is inversely related to the prognosis after hemorrhage.^{21,34,35} In addition, changes in the HVPG after a pharmacologic intervention appear to predict the clinical response to therapy.³⁶ Unfortunately, although the measurement of the HVPG is a useful adjunct, the procedure is invasive and thus may not be used in clinical practice.

SEVERITY OF VARICEAL BLEEDING

Once variceal rupture occurs, the factors which govern the severity of the bleed include the size of the hole in the varix, the pressure in the varix (TP), and the viscosity of blood. This can be expressed as:

$$\text{Severity of bleed} = \frac{(\text{TP}_1 - \text{TP}_2) \times \text{area of variceal rent}^{25}}{\text{Blood viscosity}}$$

At higher pressures and in the presence of a larger tear in the variceal wall, bleeding will be more severe. Factors influencing TP have been mentioned previously. Factors determining the size of the rent are not well defined. However, blood viscosity, which is inversely related to the hematocrit, needs to be mentioned here. Anemia resulting from blood loss, re-expansion of blood volume with intravenous fluids and the dilutional effect of high circulating levels of antidiuretic hormone, all reduce hematocrit, decrease blood viscosity, and may exacerbate bleeding.³⁷

DEFINITIONS IN THE CONTEXT OF VARICEAL BLEEDING

Consensus Committee adopted following definitions in the context of variceal bleeding:

- **Variceal Bleeding** – Bleeding from an esophageal or gastric varix at the time of endoscopy or the presence of large esophageal or gastric varices with blood in the

stomach and no other recognizable cause of bleeding⁹ and in case of absence of blood presence of esophageal or gastric varices with evidence of recent bleed in the form of cherry red spots and/or red wale marks.

- **Clinically Significant Bleeding** – when there is a transfusion requirement of 2 units of blood or more within 24 hours of the time zero, together with a systolic blood pressure of less than 100 mm of Hg or a postural change of greater than 20 mm Hg and /or pulse rate greater than 100 beats per minute at time zero (time zero is the time of admission to the first hospital the patient is taken to).⁹
- **Time frame of Acute Bleeding** – The acute bleeding is represented by an interval of 120 hours (5 days) from time zero.¹¹ Any bleeding occurring during this time interval is considered as failure to control bleeding. Any evidence of bleeding after 120 hours is the first rebleeding
- **Failure to Control Bleeding** – The definition of failure to control bleeding is divided into two time frames:⁹
 - **Within six hours** – any of the following factors:
 - Transfusion requirement of 4 units or more
 - Inability to achieve an increase in systolic blood pressure by 20 mm Hg or to 70 mm Hg or more
 - Inability to achieve a pulse rate reduction to less than 100 beat per minute
 - Reduction of 20 beat /min from baseline pulse rate
 - **After six hours** – any of the following factors:
 - Occurrence of hematemesis from the six hour point
 - Reduction in blood pressure of more than 20 mm Hg from the six hour point
 - Increase in pulse rate of more than 20 beats per minute from the six hour point on two consecutive readings an hour apart
 - Transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the hematocrit or above 27% or hemoglobin to above 9g/dl.

- Failure signifies need to change therapy; one criterion defines failure, whichever occurs first:¹¹
 - Fresh hematemesis >2h after start of specific drug treatment or therapeutic endoscopy. In the minority of patients who have a nasogastric tube in place, aspiration of greater than 100 ml of fresh blood represents failure
 - 3 g drop on Hb if no transfusion is administered
 - Death
 - Adjusted Blood Transfusion Requirement Index (ABRI) >0.75 at any time point
 - **ABRI= Blood units transfused**
(Final Hct-initial Hct) + 0.01
 - Hct (or Hb) is measured at least every
 - 6 h for the first 2 days
 - the transfusion target should be an hematocrit of 24% or a hemoglobin of 8 g/dL
- **Variceal Rebleeding** – Occurrence of new hematemesis or melena after a period of 120 hours or more from time zero (time zero is the time of admission to the first hospital the patient is taken to). All bleeding episodes regardless of severity should be counted in evaluating rebleeding.¹¹
- **Early Mortality** – Death within six weeks of the initial episode of bleeding.⁹

ASSESSMENT OF PROGNOSIS IN VARICEAL BLEEDING

Consensus Committee agreed upon that:

- No adequate prognostic model has been developed to predict outcomes (IIb: B)
- No individual characteristic sufficiently predicts prognosis (IIb: B)
- Child-Pugh class, active bleeding at endoscopy, HVPG, infection, renal failure, severity of initial bleeding, presence of portal vein thrombosis or of HCC and ALT have been identified as indicators of poor prognosis (IIb: B)

MANAGEMENT OF VARICEAL BLEEDING

Variceal hemorrhage is typically an acute clinical event characterized by severe gastrointestinal bleeding presenting as hematemesis with or without melena or hematochezia. Hemodynamic instability, tachycardia and hypotension are common. A successful outcome, as in all cases of gastrointestinal bleeding, hinges on prompt resuscitation, hemodynamic support, and correction of hemostatic dysfunction, preferably in an ICU. After stabilizing the patient hemodynamically, one should focus on the differential diagnosis. Although variceal bleeding is common in patients with cirrhosis who have acute upper GI hemorrhage, other causes of bleeding, such as ulcer disease, must be considered. Empirical pharmacological therapy is indicated in situations in which variceal bleeding is likely. Subsequently endoscopy facilitates an accurate diagnosis and endoscopic therapy. Specific management varies according to the source of variceal bleeding:

1. Esophageal varices
2. Gastric varices
3. Non-cirrhotic portal hypertension

There are no satisfactory non-endoscopic indicators of the presence of varices. While further studies are awaited, endoscopic screening is still the best practice to detect varices. The hepatic vein pressure gradient (HVPG) is presently the most reliable predictor of variceal development;¹⁰ anyhow, it is still not in clinical practice. Therefore, short of endoscopy, detailed history and good physical examination remains the most reliable tool to make the probable diagnosis of variceal bleeding. Source of upper GI bleed may be considered as variceal if:

- Patient is a diagnosed case of liver cirrhosis or non-cirrhotic portal hypertension
- No other cause like NSAIDs, peptic ulcer disease, etc is suggested by the history
- Presence of signs of liver cirrhosis and/or portal hypertension

Esophageal Varices

Management of patients with esophageal variceal bleeding includes three scenarios:

1. Treatment of acute variceal bleeding

2. Prevention of the initial bleeding (Primary Prophylaxis)
3. Prevention of re-bleeding after an initial bleeding episode (secondary Prophylaxis)

Treatment of Acute Variceal Bleeding

Consensus Committee reviewed available evidence about different therapeutic options for the treatment of acute variceal bleeding, before laying down its Recommendations.

AVAILABLE OPTIONS:

Available evidence was reviewed about the followings therapeutic modalities:

1. Pharmacological therapies
2. Endoscopic therapies
3. Balloon tamponade
4. TIPSS
5. Surgical Procedures

Pharmacological Therapies: A critical advantage of pharmacological therapies for acute hemorrhage is that they can be administered early and do not require special technical expertise. Pharmacological therapy has thus evolved into an attractive first-line approach in patients with probable variceal hemorrhage. Two major classes of drugs have been used to treat acute variceal bleeding. These include vasopressin or its analogues and Somatostatin or its analogues.

- *Vasopressin:* It reduces splanchnic blood flow and portal pressure. Studies have shown it reduces incidence of rebleeding.³⁸⁻⁴² Cardiac side effects like reduction in cardiac output and cardiac ischemia limits its use as a monotherapy; therefore it should be administered along with Nitroglycerine to counteract its cardiac side effects, well demonstrated by studies.⁴³⁻⁴⁶ Because of its short half-life, it needs to be given by continuous intravenous infusion.
- *Terlipressin:* It is a synthetic analogue of vasopressin (triglycyl lysine vasopressin) that can be given by intermittent intravenous injections. Studies suggest that it reduces mortality as compared to placebo⁴⁷⁻⁴⁹. It has comparable efficacy against

Vasopressin⁵⁰⁻⁵⁴ and Somatostatin⁵⁵⁻⁵⁷ but with very low incidence of side effects.⁵⁸ It is administered 2mg IV stat, followed by 1mg QID for 3 to 5 days.

- *Somatostatin*: It causes selective splanchnic vasoconstriction and reduces portal blood flow.⁵⁹ studies have shown its efficacy in reducing the incidence of rebleeding.⁶⁰⁻⁶⁵ It is administered as 250 ug IV bolus, followed by 250 ug per hour for 3 to 5 days.
- *Octreotide*: It is a synthetic analogue of Somatostatin that has an advantage of longer half-life (1-2 hours versus 1-2 minutes of Somatostatin). Studies have shown its efficacy in reducing the incidence of rebleeding⁶⁶⁻⁷³ It is administered as 100 ug IV bolus, followed by 25-50 ug per hour infusion.

Endoscopic Therapies: Endoscopic therapy has revolutionized the care of patients with cirrhosis who bleed from their varices. Indeed, current endoscopic therapies are capable of stopping bleeding in almost 90% of patients. Following endoscopic therapies have been used to treat acute variceal bleeding:

- *Sclerotherapy*: Endoscopic variceal sclerotherapy stops bleeding by causing thrombus formation in the bleeding varix by either intravariceal or paravariceal injection of sclerosing agent like ethanolamine oleate, absolute alcohol^{70,74}, etc. Studies have clearly demonstrated its efficacy in control of acute variceal bleeding and reduction in incidence of rebleeding^{70,74-82} The advantages of sclerotherapy include its ability to control bleeding, its wide availability, its ease of use, and its low cost. Chest pain, fever, infection, ulceration, perforation and stricture formation are the drawbacks of this procedure.
- *Variceal Band Ligation*: It is a modified technique being used for the elastic band ligation of internal hemorrhoids. It was first used in humans in 1988 by Steigmann⁸³. Studies have demonstrated its efficacy to be comparable with sclerotherapy, but with less side effects.^{84,85} That's the reason, it has replaced sclerotherapy as a gold standard.

Balloon Tamponade: It is a highly effective treatment procedure that controls acute bleeding in up to 90% of patients, but associated with 50% rebleeding and 20% other serious complications like esophageal ulceration and aspiration pneumonia⁸⁶. Therefore it

has been given up as a first line therapeutic measure; anyhow, it may be a life saving procedure in case of massive uncontrolled variceal bleeding.

TIPSS: Treatment with TIPSS consists of the vascular placement of an expandable metal stent across a tract created between a hepatic vein and a major intrahepatic branch of the portal system. TIPSS leads to hemodynamic changes similar to those that result from the placement of a partially decompressive side-to-side portacaval shunt. Although TIPSS is associated with substantially lower morbidity and mortality than surgical shunts, immediate complications such as bleeding and infection can occur. TIPSS has been proven to be highly effective treatment procedure in case of uncontrolled variceal bleeding.⁸⁷⁻⁸⁹ However, it needs advanced radiological set-up and properly trained expertise.

Surgical Procedures: These should be considered in cases of continued bleeding or recurrent early bleeding. Surgical options include H-graft portacaval shunt and esophageal staple transaction with or without esophageogastric devascularization.^{71-82, 90}

PSG RECOMMENDATIONS:

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. Considering our national scenario, patients with variceal bleeding should be managed in two phases: early and subsequent management.

Early Management of Variceal Bleeding:

The essential components include resuscitation, blood volume replacement, vasoactive drugs, prevention of associated complications, and referral for specific therapy:

Resuscitation of the patient

- The foremost important step in the management of variceal bleeding is to evaluate the patient hemodynamically. If in shock, basic **ABC** (passing **A**irway, ensuring good

Breathing, and maintaining **C**irculation – pulse and blood pressure) needs to be achieved before of anything else.

- ICU management is recommended (Recommendation grade **CII**)
- At least 2 wide bore (16 G preferably) IV cannulae should be passed
- Cross match blood – ideally 4-6 units
- NG tube may be placed

Blood volume replacement

- Blood volume restitution should be done cautiously and conservatively, using plasma expanders to maintain hemodynamic stability and PRBC to maintain the hemoglobin at approximately 8 g/dl, depending on other factors such as patients co-morbidities, age, hemodynamic status and presence of ongoing bleeding clinically (Recommendation grade **BI**)

Vasoactive drugs

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible before diagnostic endoscopy (Recommendation grade **BI**)
- Vasoactive drugs (Terlipressin, Somatostatin, Octreotide) should be maintained in patients with variceal bleeding for 2-5 days (Recommendation grade **AI**)
- Recommended dosages for the drugs are
 - Terlipressin- 2mg stat and then 1mg QID
 - Octreotide- 100 ug bolus followed by 25-50 ug per hour
 - Somatostatin- 250 ug bolus and followed by 250 ug per hour
- Pharmacological therapy in acute variceal bleeding should be started at the time of initial contact with the patient at the primary care level (Recommendation grade **CI**)
- Combination of endoscopic and pharmacological therapy should be used in patients with acute variceal bleeding (Recommendation grade **AI**).
- Pharmacological therapy alone may be acceptable in circumstances where endoscopic facilities are not available and patient has stopped bleeding with this therapy. However the patient should be referred for endoscopy and definitive therapy (EVBL) as soon as possible (Recommendation grade **CI**)

- The use of intravenous proton pump inhibitors in this setting needs further study before a recommendation can be made.

Prevention of associated complications

- *Use of antibiotics for preventing bacterial infections/spontaneous bacterial peritonitis*
 - Antibiotic prophylaxis is an integral part of therapy for patients presenting with bleeding and should be instituted from admission (Recommendation grade **AI**)
 - A third generation cephalosporin starting with parenteral and changing to oral given for 3- 7 days is adequate for this purpose Quinolones may be used as an alternative (Recommendation grade **CI**).
- *Prevention of hepatic encephalopathy*
 - In patients who present with or develop encephalopathy, this should be treated with Lactulose or other drugs (Recommendation grade **CI**)
 - There are no studies evaluating the usefulness of Lactulose for the prevention of hepatic encephalopathy, but the Committee feels that it may be considered if the treating physician wants so (Recommendation grade **CIII**)
- *Management of coagulopathy and thrombocytopenia*
 - Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data but the Committee feels that it may be considered if the treating physician wants so in some cases (Recommendation grade **CIII**)

Referral for specific therapy

- As soon as the patient is hemodynamically stable, endoscopy should be performed; and if endoscopy is not available in the center, he/she must be referred to the center where endoscopy should be performed. Till endoscopy is performed, vasoactive therapy should be continued as stated earlier.

Subsequent Management of Variceal Bleeding:

The essential components include measures to control initial bleeding and rebleeding:

Control of initial bleeding

- *Endoscopic Treatment*

- Endoscopic treatment is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause of bleeding (Recommendation grade **AI**)
- Variceal Band Ligation is the recommended form of endoscopic therapy for acute esophageal variceal bleeding although sclerotherapy may be used in the acute setting if ligation is technically difficult or unavailable (Recommendation grade **AI**)
- Endoscopic therapy with tissue adhesive (N-butyl Cyanoacrylate) is recommended for acute gastric variceal bleeding (Recommendation grade **AI**)
- Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy (Recommendation grade **AI**)

- *Balloon Tamponade*

- Balloon tamponade should only be used in massive bleeding as a temporary “bridge” until definitive treatment can be instituted (for a maximum of 24 hours preferably in an intensive care facility by personnel familiar with its use) (Recommendation grade **BI**)

Failure to control active bleeding

- Failures of initial therapy with combined pharmacological and endoscopic therapies are best managed by a second attempt at endoscopic therapy (Recommendation grade **BI**)
- Patient may be referred for TIPS or surgical intervention according to the level of expertise available in the area (Recommendation grade **BI**)
- Child A and B patients with failure to control bleeding may be referred for surgical intervention (Recommendation grade **BII**)

Primary Prophylaxis of Variceal Bleeding

Once esophageal varices have been identified in a patient with cirrhosis, the risk of variceal bleeding is 25 to 35 percent.^{1,91-93} Because of the poor outcome of variceal bleeding, the identification of those at high risk and prevention of a first bleeding episode are of critical importance. Screening endoscopy is generally recommended for patients with cirrhosis to determine whether large varices are present – although the cost effectiveness of this approach is controversial. The use of clinical features, such as increased INR, low serum albumin, a low platelet count, increased portal vein diameter, may help physicians to predict which patients are likely to have large varices.^{94,95}

Consensus Committee reviewed available evidence about different therapeutic options for primary prophylaxis of variceal bleeding, before laying down its Recommendations.

AVAILABLE OPTIONS:

Available evidence was reviewed about the following therapeutic modalities:

1. Pharmacological therapies
2. Endoscopic therapies
3. Surgical therapies

Pharmacological Therapies: Pharmacotherapy is given to reduce portal pressure and, consequently, intravariceal pressure. Drugs that reduce the collateral portal venous flow (vasoconstrictors) or intrahepatic vascular resistance (vasodilators) have been used; these include beta-blockers, nitrates, α_2 -adrenergic blockers, spironolactone, pentoxifylline, and molsidomine.⁹⁶⁻⁹⁸ Since varices are unlikely to bleed when the HVPG is less than 12mm Hg, reduction of this pressure to this level is ideal. Substantial reductions in the HVPG (by more than 20 percent) are also clinically meaningful.^{36,99-101}

- *Beta-blockers:* These reduce splanchnic blood flow, portal pressure, and subsequently gastroesophageal collateral blood flow.^{102,103} Propranolol and Nadolol, nonselective beta-blockers, are preferred because of their combined actions: blockade of β_1 -adrenergic receptors causes splanchnic vasoconstriction by means of reflex activation of α_2 -adrenergic receptors, and blockade of β_2 -adrenergic receptors results in splanchnic and peripheral vasoconstriction by

eliminating β_2 -receptor mediated vasodilatation. In the absence of a determination of the HVPG, the dose of beta-blockers is titrated on the basis of clinical measurements to achieve a resting heart rate of 55 beats per minute or a reduction of 25 percent from the base-line rate.¹⁰⁴ In addition to their side effects side effects, an important problem with beta-blockers is their variable effect on portal pressure and the consequent difficulty in predicting a clinical response.^{100, 103,105}

Beta-blockers have been found to be effective in preventing first bleed in several controlled trials.¹⁰⁶⁻¹¹² In addition, meta-analyses have revealed a 40 to 50 percent reduction in the risk of bleeding (from a 22 to 35 percent probability to a 17 to 22 percent probability; pooled odds ratio, 0.54) and a trend toward improved survival.^{91,93,113,114}

- *Isosorbide mononitrate*: Vasodilators reduce portal pressure quite effectively. Among these Isosorbide mononitrate has received the greatest attention because of its long half-life (approximately 5 hours). A comparing trial showed no significant difference between isorbide mononitrate and Propranolol.¹¹⁵ Anyhow, it cannot currently be recommended as monotherapy, because of its potential to accentuate the vasodilative hemodynamics typical of cirrhosis.^{116,117}
- *Combination of beta-blockers & Isosorbide mononitrate*: In one study, combination of Isosorbide mononitrate to Propranolol caused 20% reduction in the HVPG in 50% of patients as compared to only 10% patients by Propranolol alone.¹¹⁸ In another study, in patients with cirrhosis of Child-Pugh class A and B, combination of Isosorbide mononitrate to Nadolol reduced incidence of initial bleeding 50% greater than Nadolol alone.¹¹⁹

Endoscopic Therapies: Two main endoscopic procedures – sclerotherapy and variceal band ligation have been used to treat prevent first episode of variceal bleeding:

- *Sclerotherapy*: Trials have reported variable results in terms of primary prophylaxis of variceal bleeding.^{111,112,120-136} These trials are also different from one another regarding size of varices, type of sclerosing agent, and technique of injection. Two trials showed a significant reduction in both bleeding and mortality.^{122,123} One trial didn't prevent bleeding but reduced the mortality.¹³⁰ One

trial significantly increased the risk of bleeding¹²⁷ and another one that of mortality.¹³³ Because of this marked heterogeneity between these trials, a meta-analysis is clinically inappropriate. At present time, sclerotherapy cannot be recommended for the primary prophylaxis of variceal bleeding.

- *Variceal Band Ligation:* It has been favored in many trials for primary prophylaxis of variceal bleeding because it is as effective as sclerotherapy but leads to fewer complications.¹³⁷⁻¹³⁹ Another randomized comparative trial favored band ligation against Propranolol in reducing incidence of first bleed without affecting mortality.¹⁴⁰ Variceal ligation has become an acceptable option for primary prophylaxis in patients where medical therapy is contraindicated or intolerant. Studies are needed to evaluate its possible role as an adjunct to pharmacologic therapy.

Surgical Therapies: Two types of surgical therapies have been documented:

- *Portacaval shunts:* A meta-analysis of trials comparing portacaval shunts against non-active treatment showed a significant benefit in the reduction of variceal bleeding (odds ratio 0.31, 95% CI 0.17 – 0.56) but also a significantly greater risk of hepatic encephalopathy (odds ratio 2, 95% 1.2 – 3.1) and of mortality (odds ratio 1.6, 95% CI 1.02 – 2.57) in patients treated with shunt surgery.¹⁴¹⁻¹⁴⁴
- *Devascularization procedures:* One trial showed that there was a significant reduction in variceal bleeding and in mortality in patients treated with a variety of devascularization procedures; anyhow these results need to be confirmed in further studies as in this trial different procedures were used in each of the 22 centers.¹⁴⁵

PSG RECOMMENDATIONS:

- All patients with cirrhosis should be endoscoped at the time of diagnosis (Recommendation grade **AI**). If at the time of endoscopy:
 - No varices are found, surveillance endoscopies should be performed every three years (Recommendation grade **AII**)

- Grade 1 varices are found, surveillance endoscopies should be performed every year (Recommendation grade **AII**). Primary prophylaxis with beta-blockers may be considered in some cases, especially in the presence of red wale signs or Child class C (Recommendation grade **CIII**); there is limited level of evidence, studies are needed before formal recommendation.
- Grade 2 varices are found and patient is in Child class B or C, primary prophylaxis should be given (Recommendation grade **BI**)
- Grade 3 varices are found, primary prophylaxis should be given irrespective of the severity of cirrhosis (Recommendation grade **AI**)
- In patients with decompensated cirrhosis – i.e. patients with jaundice, ascites, and encephalopathy, primary prophylaxis may be started prior to the endoscopic confirmation of esophageal varices (Recommendation grade **CIII**)
- In case if endoscopic facilities are not available, primary prophylaxis may be given if the following indirect parameters are present (Recommendation grade **CIII**)
 - INR > 1.5
 - Bilirubin > 2mg/dl
 - Albumin <28 gm/L
 - Platelet count < 70 x 10⁹ /L
 - Portal vein diameter > 13 mm on abdominal ultrasound
- *Pharmacological therapy* (non-selective beta-blockers therapy) is the best available modality of primary prophylaxis at present (Recommendation grade **AI**).
 - Propranolol or Nadolol are the drugs of choice (Recommendation grade **AI**).
 - Aim of the therapy is to reduce the HVPG to less than 12 mm. Hg (Recommendation grade **AI**).
 - Propranolol should be started at the dose of 40 mg twice daily (Recommendation grade **AI**)
 - Nadolol should be started at the dose of 20 mg at bed time (Recommendation grade **AI**)
 - Dose should be adjusted in an incremental fashion to reduce the heart rate by 25 % or to 55 beats per minute (Recommendation grade **AI**)

- Isosorbide mononitrate must not be used alone. There is also not enough data to recommend the combination therapy of nitrates or spironolactone with beta-blockers in primary prophylaxis. Similarly, other drugs like Losartan-K, Pentoxifylline, Metoclopramide, Verapamil, Molsidomine and Clonidine must be adequately tested before formal use in primary prophylaxis.
- In case of contraindications or intolerance to beta-blockers, variceal band ligation is the treatment of choice for grade 2 and larger varices (Recommendation grade **AI**)
 - Ligation should be performed every 2 to 8 weeks until the varices have been eradicated (Recommendation grade **AI**)
- Variceal band ligation and beta-blocker combination therapy may be used in high risk varices (Recommendation grade **CI**).
- In difficult situations where neither Propranolol nor variceal band ligation can be used, isosorbide mononitrate is the treatment of choice in the dose of 20 mg twice daily (Recommendation grade **BI**)
- Sclerotherapy, TIPSS and surgical therapies are not recommended in primary prophylaxis

Secondary Prophylaxis of Variceal Bleeding

Variceal bleeding recurs in approximately two-thirds of patients, most commonly within the first six weeks after the initial episode.¹⁴⁶⁻¹⁴⁸ Clinical predictors of early recurrence include: 1) severity of the initial hemorrhage i.e., the development of hypotension or a substantial transfusion requirement, 2) degree of liver decompensation, and 3) the presence of encephalopathy and impaired renal function.¹⁴⁹ Endoscopic predictors of early recurrence include: 1) active bleeding at the time of initial endoscopy, 2) stigmata of recent bleeding, and 3) large varices.^{149,150} In addition, severity of portal hypertension, measured by the HVPG, correlates closely with the risk of rebleeding as well as with the actuarial survival rate after an initial variceal bleeding.^{35,151} Because of the risk of rebleeding and its associated morbidity and mortality, secondary prophylaxis must be given after the initial episode of variceal bleeding.

Consensus Committee reviewed available evidence about different therapeutic options for secondary prophylaxis of variceal bleeding, before laying down its Recommendations.

AVAILABLE OPTIONS:

Available evidence was reviewed about the following therapeutic modalities:

1. Pharmacological therapies
2. Endoscopic therapies
3. TIPSS
4. Surgical therapies

Pharmacological Therapies: Reducing the portal pressure by more than 20 percent from the base-line value pharmacologically results in a reduction in the cumulative probability of recurrent bleeding from 28% at one year, 39% at two years, and 66 percent at three years to 4%, 9%, and 9% respectively.¹⁰⁰ Although adjusting medical therapy on the basis of a measurement of portal pressure would be ideal, the means to determine the HVPG are not readily available; thus, therapy must be adjusted with the use of empirical clinical variables.

Many pharmacological agents have been proposed for use in secondary prophylaxis,⁹⁶⁻⁹⁸ but beta-blockers have been found to be the most effective in decreasing the risk of rebleeding and prolonging survival.¹⁵²⁻¹⁵⁵ Combination of beta-blockers and isosorbide mononitrate has been found to be superior to beta-blockers alone in preventing rebleed¹⁵⁶ but offers no survival advantage and reduces the tolerability of therapy. Combination of Nadolol and isosorbide mononitrate has been found to be superior to sclerotherapy in preventing rebleed along with improved survival advantage in Child class A and B.¹⁰¹ Combination of Nadolol and isosorbide mononitrate has been found to be superior to variceal band ligation in preventing rebleed along with improved survival advantage in Child class A and B.¹⁵⁷

Endoscopic Therapies: Two main endoscopic procedures – sclerotherapy and variceal band ligation have been used to treat prevent recurrence of variceal bleeding:

- *Sclerotherapy:* Sclerotherapy reduces the risk of recurrence of variceal bleeding but it does not appear to reduce overall mortality.¹⁵⁸⁻¹⁶⁸ A meta-analysis of nine trials found sclerotherapy and beta-blockers to be equivalent regarding reduction

recurrence of bleeding and survival.¹⁶⁹ Moreover combination of beta-blocker and isosorbide mononitrate was superior to sclerotherapy alone in patients with Child class A and B.¹⁰¹

- *Variceal Band Ligation:* It has been favored in many trials for secondary prophylaxis of variceal bleeding because it is as effective as sclerotherapy but leads to fewer complications.^{158,159,170,171}
- *Combination therapies:* Combination of sclerotherapy and beta-blocker was superior to beta-blocker alone but provided no survival benefit.^{172,173} Combination of band ligation and Nadolol was superior to ligation alone but provided no survival benefit.¹⁷⁴ Combination of sclerotherapy and band ligation has not been favored.^{175,176}

TIPSS: Studies have shown TIPSS to be more effective than endoscopic therapy in preventing rebleeding¹⁷⁷⁻¹⁸⁷ but there is increased incidence of clinically significant encephalopathy^{188,189} and no survival benefit over endoscopic therapy, rather patients with advanced liver disease may have poor outcome.¹⁹⁰⁻¹⁹² Therefore, TIPSS is best used as a bridge to liver transplantation. Stenosis of shunt occurs in 31% at one year and 47% at two years.^{193,194} Doppler studies may be used to evaluate patency of the shunt, but it has extremely low sensitivity and specificity.¹⁹⁵ An analysis comparing overall cost of TIPSS with that of sclerotherapy found no difference between these two procedures.¹⁹⁶

Surgical Therapies: Two types of surgical therapies have been documented:

- *Portacaval shunts:* These may be either non-selective or selective:
- Non-selective shunts – divert portal blood flow into the systemic circulation thereby reducing liver blood flow. Studies have shown significant reduction in rebleeding with these shunts.¹⁹⁷⁻²⁰⁰
- Selective shunts – e.g., distal splenorenal shunt, drain varices into systemic circulation without affecting liver blood flow. Studies have found these to be comparable with non-selective shunts in terms of efficacy, complications, and mortality.²⁰¹⁻²⁰⁶

Shunt surgery has been found to be effective than sclerotherapy but associated with significantly greater incidence of encephalopathy.²⁰⁷⁻²¹² Rates of rebleeding range from 10 to 20 percent, with the highest risk occurring during the first month after surgery.^{209,210}

- *Devascularization procedures:* Devascularization procedures e.g., esophageal transection and devascularization are usually considered in patients who cannot receive shunts because of splanchnic venous thrombosis and should be performed only by experienced surgeons.¹⁰⁴

PSG RECOMMENDATIONS:

- After the control of acute variceal bleeding, secondary prophylaxis must be given to all patients (Recommendation grade **AI**)
- Secondary prophylaxis should be started as soon as possible from day 6 of the index variceal bleeding episode. The time of start of secondary prophylaxis should be documented (Recommendation **CIII**)
- Combination of beta-blockers and endoscopic variceal ligation is the treatment of choice, unless beta-blockers are contraindicated (Recommendation grade **AII**)
- Ligation should be performed every 4 weeks until the varices have been eradicated (Recommendation grade **AI**)
- Following successful eradication of varices, patients should be endoscoped at three months and six monthly thereafter to look for recurrence of varices. In case of recurrence, band ligation should be repeated (Recommendation grade **AII**)
- If band ligation is not available, sclerotherapy should be the alternative (Recommendation grade **B1**)
- The interval between treatments should be the same as outlined for band ligation. The sclerosing agents used may vary between institutions (Recommendation grade **AII**)
- Non-selective beta-blockers therapy, in combination with endoscopic therapy or alone, should be given as discussed earlier in primary prophylaxis:
 - Propranolol or Nadolol are the drugs of choice (Recommendation grade **AI**).
 - Aim of the therapy is to reduce the HVPG to less than 12 mm. Hg (Recommendation grade **AI**).

- Propranolol should be started at the dose of 40 mg twice daily (Recommendation grade **AI**)
 - Nadolol should be started at the dose of 20 mg at bed time (Recommendation grade **AI**)
 - Dose should be adjusted in an incremental fashion to reduce the heart rate by 25 % or to 55 beats per minute (Recommendation grade **AI**)
- In patients who fail endoscopic and beta-blockers therapy:
 - TIPSS and surgical shunts (distal splenorenal shunt or 8 mm H-graft) therapies are the procedures of choice in Child class A/B
 - Liver transplantation is procedure of choice in Child class B/C; anyhow TIPSS may be used as a bridge to liver transplantation
 - However these options may be used in selected center with particular expertise (Recommendation grade **AI**)

Gastric Varices

Management of patients with gastric variceal bleeding needs to be dealt separately, as gastric varices differ significantly from esophageal varices.

CLASSIFICATION OF GASTRIC VARICES: Gastric varices can be classified into two on the basis of its development:

- *Primary gastric varices* – are those gastric varices that develop spontaneously and are detected at the first endoscopy. These occur in 20% of patients with all types of portal hypertension but are more commonly observed in patients with portal hypertension due to extrahepatic portal vein obstruction compared with cirrhosis.
- *Secondary gastric varices* – are those gastric varices that develop as a result of redistribution of portal hypertension after eradication of esophageal varices and are detected within two years of eradication of esophageal varices. These occur in 10% of patients with all types of portal hypertension but are more commonly observed in patients with cirrhosis.^{213,214}

TYPES OF GASTRIC VARICES: Gastric varices can be classified basically into two types on the basis of their location in the stomach and relationship with esophageal varices. Management depends upon the type of gastric varices:

- *Gastro-Oesophageal Varices (GOV)* – are those gastric varices that are continuous with esophageal varices and extend for 2-5 cm below the gastroesophageal junction:

- along the along the lesser curvature of the stomach (GOV1), or
- into the fundus of the stomach (GOV2)

GOV1 are the most common type of varices seen in cirrhosis.

- *Isolated Gastric Varices (IGV)* – are those gastric varices that are discontinuous from the esophageal varices and occur:

- either in the fundus of the stomach (IGV1),
- or anywhere else in the stomach including the body, antrum, pylorus, and duodenum²¹³

Bleeding from IGV is more fatal than bleeding from GOV.²¹⁵

MANAGEMENT OF GASTRIC VARICEAL BLEEDING:

Consensus Committee reviewed available evidence about different therapeutic options for the treatment of gastric variceal bleeding, before laying down its Recommendations.

AVAILABLE OPTIONS:

Available evidence was reviewed about the followings therapeutic modalities:

1. Endoscopic therapies
2. Surgery
3. Sengstaken tube
4. Radiology
5. TIPSS

Endoscopic Therapies: These include the followings:

- *Endoscopic sclerotherapy:* It as described for esophageal variceal bleeding has been shown to be effective in controlling active bleeding from all types of gastric

varices in about 70-80% of patients with gastric variceal bleeding.^{216,217} However, active bleeding was arrested with sclerotherapy in only 26% of patients with IGTV.²¹⁸ In addition, rebleeding after endoscopic sclerotherapy occurred in 60-90% of patients in the different studies. Episodes of rebleeding are more common in patients with IGTV.²¹⁶⁻²¹⁸

- *Endoscopic injection therapy with “super glue”*: Several studies have proved the efficacy of cyanoacrylate for the treatment of esophageogastric varices. Active bleeding was successfully controlled in 90% of patients but 50% patients had rebleeding.²¹⁹⁻²²¹
- *Endoscopic injection of thrombin*: Injection of bovine thrombin (1000 U/ml) has been found to be 100% effective in controlling active bleeding with eradication of varices after a mean of two injections. Rebleeding occurred in one out of eleven patients over a follow up of nine months.²²²
- *Endoscopic band ligation*: Gastric variceal band ligation using “O” rings and detachable snares have been shown to control active bleeding from gastric varices but is followed almost invariably rebleeding.^{223,224} No controlled data are available on the use of this treatment approach. However, given the anatomy of gastric varices, it may be dangerous to band them.

Sengstaken tube: Several studies have found Sengstaken-Blakemore tube to effectively control active bleeding from all types of gastric varices except IGTV2. However, rebleeding is almost universal if another modality of treatment is not instituted.^{86,213,215,225}

Surgery: Different surgical therapies have been used:

- *Under running of gastric varices* – has been shown to control active bleeding but is followed by rebleeding in 50% of patients and is associated with a perioperative mortality of greater than 40%.²²⁶
- *Complete devascularization* – of the cardia, stomach, and distal esophagus for bleeding from gastric varices is associated with good control of bleeding but is followed by rebleeding over 40% of patients and early mortality in about 50%.²²⁷

- *Distal splenorenal shunt* – effectively controlled bleeding from gastric varices in all six patients but two of the patients died in the postoperative period.²²⁸

Radiology: The use of “balloon occluded retrograde transvenous obliteration” (B-RTO) for the treatment of bleeding gastric varices has been pioneered by the Japanese.^{229,230} In this procedure, a balloon catheter is inserted via the femoral or internal jugular vein into an outflow shunt (gastric-renal or gastric-inferior vena caval). Blood flow is blocked by inflation of the balloon and then 5% ethanolamine oleate iopamidol is injected in a retrograde manner. This technique has been used in about 60 patients. Good control of bleeding was observed in all patients with rebleeding in about 10% of patients. However, no controlled data for the use of this technique are available.

TIPSS: TIPSS has been shown to control active bleeding from gastric varices in almost all patients in whom the shunt can be performed successfully.^{89,231,232} Procedure related mortality is about 1% and rebleeding occurs with shunt insufficiency in about 15% of patients.²³² In a comparative study, evaluating the clinical outcome of patients treated with TIPSS for variceal bleeding from esophageal and gastric varices, no significant differences were detected in the rate of control of bleeding, rebleeding, or survival.²³² TIPSS appears to be an effective method of treating gastric variceal bleeding. However, no randomized clinical trials comparing TIPSS with any other form of therapy are available.

PSG RECOMMENDATIONS:

Gastric variceal bleeding is characterized by massive bleeding that is more severe than esophageal variceal bleeding. The essential components of early management include resuscitation, blood volume replacement, vasoactive drugs, prevention of associated complications, and referral for specific therapy which really depends upon the type of bleeding gastric varices:

- **GOVI:** may be treated with cyanoacrylate; otherwise treatment of the esophageal varices by EVL/ Sclerotherapy is sufficient (Recommendation grade **BII**)

- **GOV2 and IGV:** treat initially with N-butyl-2-cyanoacrylate (Recommendation grade **AI**). In case of failure to control bleeding, balloon tamponade with Sengstaken-Blakemore tube (Recommendation grade **BII**). In case of recurrence of gastric varices, TIPSS or shunt surgery (Recommendation grade **BII**)

Bleeding from portal hypertensive gastropathy – may be treated with beta-blockers along with other general measures. Laser therapy may be of help if available. TIPSS may be needed long-term.¹¹

Non-cirrhotic portal hypertension

Two main scenarios need to be considered:

Budd-Chiari Syndrome (BCS):

Definition – Budd-Chiari Syndrome means hepatic venous outflow obstruction

Etiology – BCS may be primary or secondary. Compression/invasion by a benign or malignant tumor, abscess or cyst, myeloproliferative disorders, and thrombosis results in secondary Budd-Chiari Syndrome.

Diagnosis – BCS is diagnosed by the demonstration of an obstruction of the venous lumen, or by the presence of hepatic vein collaterals. Liver biopsy is not necessary, except in case of BCS of the small intrahepatic veins.

Treatment – It was agreed upon that:

- Complications of portal hypertension may be treated as recommended for other types of liver diseases.
- For the control of acute variceal bleeding, endoscopic therapy is effective (Recommendation grade **AII**).
- Anticoagulation should be recommended to all patients, in the absence of major contra-indications. However, there is no consensus on the optimal duration of anticoagulation.

- Previous bleeding related to portal hypertension is not considered a major contraindication for anticoagulation, provided appropriate prophylaxis for recurrent bleeding is initiated.
- Stenosis that is amenable to percutaneous angioplasty or stenting should be actively looked for, and treated accordingly.
- TIPSS insertion should be attempted when angioplasty or Stenosis is not feasible, and when the patient does not improve on medical therapy.
- Liver transplantation should be considered in patients with manifestation refractory to the above procedures.¹¹

Extrahepatic portal vein obstruction (EHPVO):

Definition – EHPVO is defined by obstruction of the extra-hepatic portal vein, mainly by thrombosis. It may be associated with cirrhosis and neoplasia.

Diagnosis – EHPVO is diagnosed by imaging techniques like Doppler US, CT or MRI which demonstrate portal vein obstruction, presence of intraluminal material or portal vein cavernoma.

Treatment – depends upon the clinical presentation:

Acute EHPVO:

- It rarely resolves spontaneously
- Anticoagulation should be given for at least 3 months in all patients, life-long in case of underlying persistent prothrombotic state (Recommendation grade **CIII**)
- In case of cirrhosis and EHPVO, hepatocellular carcinoma should be excluded.

Chronic EHPVO:

- For primary prophylaxis of variceal bleeding, data is insufficient to prefer beta-blockers or endoscopic therapies
- For the control of acute variceal bleeding, endoscopic therapy is effective. In the absence of specific data on patients with EHPVO, it is presumed that the same treatments used in bleeding cirrhotic patients could be applied (Recommendation grade **CIII**)
- For secondary prophylaxis of variceal bleeding, endoscopic therapy is effective. There is insufficient evidence to recommend beta-blockers.

- There is no consensus on the indication for anticoagulation therapy. However, in those patients with a persistent documented prothrombotic state, anticoagulation therapy can be considered
- Evidence is insufficient for TIPSS and local thrombolysis.
- Decompressive surgery should be only considered for patients with failure of endoscopic therapy (Recommendation grade **CIII**)¹¹

ROLE OF ANTIBIOTICS IN VARICEAL BLEEDING

Studies have reported bacterial infections to occur in about 20% of patients with cirrhosis with upper gastrointestinal bleeding within 2 days and 35-66% within two weeks of admission into hospital.²³³⁻²³⁶ Bacterial infections are closely related to prognosis in terms of failure to control bleeding, rebleeding and in-hospital outcome.²³⁴⁻²³⁶ Studies have compared antibiotics prophylaxis with no treatment in patients with acute variceal bleeding.²³⁷⁻²⁴³ Fluoroquinolones were used in four trials,²³⁷⁻²⁴¹ amoxicillin and clavulanic acid in two trials,^{239,240} and oral non-absorbable antibiotics in one.²³⁷ The results show that antibiotic prophylaxis resulted in significantly lower rate of infection, bacteraemia, spontaneous bacterial peritonitis, and significantly improved short term survival (mean improvement rate 9.1% [95% CI 2.9-15.3]; p<0.004). Therefore, patients with cirrhosis and upper gastrointestinal bleeding should have antibiotic prophylaxis. Most of the studies recommend Ciprofloxacin 500 mg twice daily for 7 days at least.

AREAS REQUIRING FURTHER STUDIES

Consensus committee feels that the following areas need further studies:

- Optimal duration of vasoactive drug therapy should be better defined
- Development of facilities for TIPS and liver transplant should be considered
- Effectiveness of early TIPS placement and of covered stents needs to be better studied
- Best treatment of gastric varices (especially glue vs. TIPS) needs to be defined
- The best treatment of patients with no active bleeding at time of endoscopy on drug therapy

- Prognostic factors / models for acute bleeding MELD score, variceal size, age, etiology of portal hypertension and other co morbidities
- Incidence and natural history of varices and variceal bleeding – local data needs to be generated.

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Table – 1: Grading of Evidence

Grade	Description
Grade Ia	Evidence obtained from meta-analysis of randomized trials
Grade Ib	Evidence obtained from at least one randomized trial
Grade IIa	Evidence obtained from at least one well designed controlled study without randomization
Grade IIb	Evidence obtained from at least one other type of well designed quasi experimental study
Grade III	Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies and case studies
Grade IV	Evidence obtained from expert committee reports, or opinions or clinical experiences of respected authorities

Table – 2: Grading of Recommendations for Clinical Practice

Grade	Strength of evidence to guide clinical practice
<p>A</p>	<p><i>Supported by two or more level I studies without conflicting evidence from other level I studies</i></p> <p>AI: The Committee recommends this element of care strongly</p> <p>AII: The Committee considers this element of care as moderately important</p> <p>AIII: Recommendation in this category are unlikely</p>
<p>B</p>	<p><i>Supported by two or more level I studies with conflicting evidence from other level I studies or supported by only one level I or two or more level II studies</i></p> <p>BI: The Committee considers this element of is very important</p> <p>BII: The Committee considers this element of care as moderately important</p> <p>BIII: The Committee feels this element of care is not practically important, but may be considered in some cases</p>
<p>C</p>	<p><i>Supported by level III-IV evidence</i></p> <p>AI: The Committee feels this element of care is very important</p> <p>AII: The Committee considers this element of care as moderately important</p> <p>AIII: The Committee feels this element of care is relatively unimportant, although may be considered in some cases</p>

Table – 3: Child-Pugh classification of the severity of cirrhosis

Variable	Score		
	1 point	2 points	3 points
Encephalopathy	Absent	Mild to moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dl)*	<2	2-3	>3
Albumin (g/L)	>3.5	2.8-3.5	<2.8
Prothrombin Time (sec above normal)	1-4	4-6	>6

If the total score is 5 or 6, the cirrhosis is designated as class A; if the score is 7 to 9, the cirrhosis is class B; if the score is 10 or higher, the cirrhosis is class C.

*To convert values for bilirubin to $\mu\text{mol} / \text{L}$, multiply by 17.1