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Javed Iqbal Farooqi

Hasnain Ali Shah

Aga Khan University, hasnain.alishah@aku.edu

Anwaar A. Khan

Amjad Salamat

Altaf Alam

See next page for additional authors

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Clinical Practice Guidelines on the Management of Variceal Bleeding

Javed Iqbal Farooqi¹, Hasnain Ali Shah², Anwaar A. Khan³, Amjad Salamat⁴, Altaf Alam⁵, Abbas Khan Khattak¹, Nazish Butt⁶, Muhammed Salih⁷, Sher Rehman⁸, Arif Amir Nawaz⁹, Nasir Khokhar⁸, Ghias-un-Nabi Tayyab¹⁰, Javed Aslam Butt¹¹, Kashif Malik⁵, Shakeel Ahmad Mirza¹² and Mohammad Akram¹³

These Clinical Practice Guidelines (CPGs) have been developed by Pakistan Society of Hepatology (PSH) and Pakistan Society of Study of Liver Diseases (PSSLD).

Gastroesophageal variceal bleeding is a major complication of portal hypertension resulting from cirrhosis. It occurs in 25 - 35 percent of patients with cirrhosis and accounts for 80 - 90 percent bleeding episodes in these patients. Up to 30% of initial bleeding episodes are fatal and as many as 70% of survivors have recurrent bleeding within one year.

Screening for varices:

Ideally, all patients should undergo screening upper Gastrointestinal (GI) endoscopy for varices at the time of initial diagnosis of cirrhosis. If patient have no varices, repeat endoscopy should be done every 2 years in case of compensated cirrhosis and annual in case of decompensated cirrhosis. HVPG needs further study to select patients for different therapies.

Pre-primary prophylaxis of varices:

Treatment of the underlying cause of cirrhosis should be

undertaken to prevent the development of portal hypertension or reduce already developed portal hypertension in an attempt to prevent the development of varices. At present, β -blockers are not recommended to be used for pre-primary prophylaxis of varices.

Primary prophylaxis of varices:

Patient with cirrhosis and small esophageal varices:

In high-risk small esophageal varices, Non-Selective β -Blocker (NSBB) should be used. In low-risk small esophageal varices, NSBB may be used if desired by the treating physician. Nitrates alone or in combination with NSBB are not recommended. Endoscopic Variceal Band Ligation (EVBL) is not recommended in the primary prophylaxis of small esophageal varices. Repeat endoscopy should be done every 2 years in case of compensated cirrhosis and annually in case of decompensated cirrhosis.

Patients with cirrhosis and medium or large esophageal varices:

Primary Prophylaxis must be given in the form of NSBB or EVBL. Choice of treatment should be based on local resources and expertise, physician/patient preference, side effects, and contra-indications. Carvedilol is an emerging and effective alternative β -blocker. Nitrates alone or with β -blockers should not be used for primary prophylaxis of variceal bleeding. There is no role of Endoscopic Injection Sclerotherapy (EIS), TIPSS and/or shunt surgery.

Primary prophylaxis of gastric varices: The risk of first bleeding from gastric varices is no greater than that from esophageal varices. Data on the prevention of the first bleeding in patients with gastric varices is sparse. It is conceivable that beta-blocker therapy is equally effective in this situation. The efficacy of cyanoacrylate in these patients remains controversial.

Management of acute variceal bleeding:

Resuscitation: ICU management is recommended. Endotracheal Tube (ET) intubation may be considered in a patient if in shock, mental status change, continuous heavy bleeding, and respiratory compromise. Nasogastric (NG) tube may be placed in selected patients with active bleeding for clearing the field of vision and monitoring of continuous bleeding. Balloon tamponade should only be used as a temporary "bridge" by trained personnel until definitive treatment can be

¹ Department of Medicine, Government Lady Reading Hospital, Peshawar.

² Department of Medicine, The Aga Khan University Hospital, Karachi.

³ Department of Gastroenterologist, Doctors Hospital, Peshawar.

⁴ Department of Gastroenterology, Military Hospital, Rawalpindi.

⁵ Department of Gastroenterology, Shaikh Zayed Hospital, Lahore.

⁶ Department of Gastroenterology, Jinnah Postgraduate Medical Centre, Karachi.

⁷ Department of Gastroenterology, Shifa International Hospital, Islamabad.

⁸ Department of Gastroenterology, Hayatabad Medical Complex, Peshawar.

⁹ Department of Gastroenterology, Fatima Memorial Hospital, Lahore.

¹⁰ Department of Gastroenterology, Postgraduate Medical Institute, Lahore.

¹¹ Kalsoom International Hospital, Islamabad.

¹² Retired Military Hospital, Rawalpindi.

¹³ Ex Gastroenterologist, Jinnah Postgraduate Medical Centre, Karachi.

Correspondence: Prof. Dr. Javed Iqbal Farooqi, Chairman Experts Meeting, Bhurban, Pakistan.

E-mail: dr_farooqi@hotmail.com

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instituted, for a maximum of 24 hours, and preferably in an intensive care facility.

Blood volume replacement: Blood volume restitution should be done cautiously and conservatively, using plasma expanders to maintain hemodynamic stability and packed red blood cells to maintain the hemoglobin at approximately 7 - 8 g/dl, depending on other factors such as patient's co-morbidities, age, hemodynamic status and presence of ongoing bleeding clinically. Colloids may be used cautiously while awaiting availability of blood and blood products.

Vasoactive agents: In suspected variceal bleeding, vasoactive agents should be started as soon as possible, before endoscopy. The efficacy of Terlipressin is equal to Octreotide as an adjuvant therapy for the control of esophageal variceal bleeding and in-hospital survival. In patients with esophageal variceal bleeding, a 24-hour course of Terlipressin is as effective as a 72-hour course when used as an adjunct to successful EVBL. 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. At the primary care level, pharmacological therapy should be started at the time of initial contact with the patient.

Bacterial infections: Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted from admission. Intravenous Ceftriaxone / oral quinolones are recommended for most patients. Intravenous Ceftriaxone is preferable in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis.

Hepatic encephalopathy: Recommendations regarding the management and prevention of encephalopathy in patients with cirrhosis and upper GI bleeding cannot be made on the basis of currently available data. It is best left to the choice of caring physician.

Coagulopathy and thrombocytopenia: Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data; it may be considered if the platelets count is less than 50,000 /cmm. PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis.

Specific therapy: Patients with GI bleeding and features suggesting cirrhosis should have upper endoscopy as soon as possible after admission (within 12 hours) after hemodynamic stabilization with airway control. Endoscopic therapy is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause

of bleeding. Endoscopic Variceal Band Ligation (EVBL) is the recommended form of endoscopic therapy for acute esophageal variceal bleeding, although sclerotherapy may be used in acute setting if ligation is technically difficult. Endoscopic Injection Sclerotherapy (EIS) with tissue adhesive (e.g. N-butyl-cyanoacrylate) is recommended for acute bleeding from Isolated Gastric Varices (IGV) and those Gastro-Esophageal Varices type-2 (GEV-2) that extend beyond the cardia. EVBL or EIS with tissue adhesive can be used in bleeding from Gastroesophageal Varices type-1 (GEV-1). Combination of pharmacological and endoscopic therapy is the most rational approach in the treatment of acute variceal hemorrhage.

Early TIPSS: An early TIPSS within 72 hours (ideally 24 hours) should be considered in patients at high-risk of treatment failure (e.g. CTP class C <14 points or CTP class B, or with active bleeding) after initial pharmacological and endoscopic therapy. HVPG measurements may be helpful to select patients for early TIPSS.

Treatment failures:

Refractory bleeding: Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by TIPSS with PTFE-covered stents. 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). Surgery may be considered in the absence of facilities for TIPS in select patients (child A cirrhosis with acute, uncontrolled variceal bleeding). Emergency surgical portocaval shunt (within 8 hours of onset of bleeding) has been reported to be associated with almost universal control of bleeding and a low mortality over a 30-year period. Uncontrolled data suggest that self-expanding covered esophageal metal stents may be an option in refractory esophageal variceal bleeding, although further evaluation is needed.

Re-bleeding:

During the first 5 days it may be managed by a second attempt at endoscopic therapy. If re-bleeding is severe, PTFE-covered TIPSS is likely the best option.

Secondary prophylaxis of varices:

After the control of acute variceal bleeding, secondary prophylaxis must be given to all patients. Patients who required shunt surgery/TIPSS to control the acute episode do not require further preventive measures. All these patients should be referred to a transplant center, if they are otherwise a candidate (i.e., CTP score ≥ 7 or a MELD score ≥ 15).

Secondary prophylaxis should be started as soon as possible from day 6 of the index variceal bleeding episode or at the time of discharge. Combination NSBB and endoscopic variceal ligation is the treatment of

choice for secondary prophylaxis. If endoscopy is not possible, BB alone or in combination with ISMN should be given. If BB are contraindicated then EVL is the preferred treatment.

Propranolol and Nadolol have been extensively studied; however Carvedilol is an emerging alternative. Carvedilol may be started at a dose of 6.25 mg daily and increased to 6.25 mg twice daily, if clinically tolerated. Carvedilol is as effective as Nadolol plus Isorsorbide-5-Mononitrate in the prevention of gastroesophageal variceal rebleeding with fewer severe adverse events and similar survival.

EVBL should be repeated every 2 - 4 weeks until obliteration. Following successful eradication of varices, patients should be endoscoped at three months and six months intervals thereafter to look for recurrence of varices. In case of recurrence, band ligation should be repeated.

TIPSS may be considered in Child A or B patients who have recurrent variceal bleed despite combination of pharmacological and endoscopic therapy as secondary prophylaxis. Surgical shunts may be considered in Child A / selected Child B patients as an alternative, if TIPSS is unavailable. Transplantation provides good long term outcome in appropriate candidates and should be considered. TIPSS may be used as a bridge to transplantation.

Treatment of GEV-1 by EVL or BB is sufficient. GEV-1 may be treated with cyanoacrylate injection. After the acute episode, patients with GEV-2/IGV-1 should receive beta blockers along with repeated sessions of CA injection or TIPSS. There is a lack of good quality data to establish the actual place of BRTO in the secondary prophylaxis bleeding from GV. BB should be used for prevention of recurrent bleeding in portal hypertensive gastropathy.

Guidelines available on JCPSP website.

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ABSTRACT

Gastroesophageal variceal bleeding occurs in 30 - 50% of patients of liver cirrhosis with portal hypertension, with 20-70% mortality in one year. Therefore, it is essential to screen these patients for varices and prevent first episode of bleeding by treating them with β -blockers or endoscopic variceal band ligation. Ideally, the 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. Proper management of such patients include: initial assessment, resuscitation, blood volume replacement, vasoactive agents, prevention of associated complications such as bacterial infections, hepatic encephalopathy, coagulopathy and thrombocytopenia, and specific therapy. Rebleeding occurs in about 60% patients within 2 years of their recovery from first variceal bleeding episode, with 33% mortality. Therefore, it is mandatory that all such patients must be started on combination of β -blockers and band ligation to prevent recurrence of bleeding. Patients who required shunt surgery/TIPSS to control the acute episode do not require further preventive measures. These clinical practice guidelines (CPGs) have been jointly developed by Pakistan Society of Hepatology (PSH) and Pakistan Society of Study of Liver Diseases (PSSLD).

Key Words: *Variceal bleeding. Re-bleeding. Gastroesophageal varices. Guidelines. Pakistan Society of Hepatology (PSH). Pakistan Society of Study of Liver Diseases (PSSLD).*

¹ Department of Medicine, Government Lady Reading Hospital, Peshawar.

² Department of Medicine, The Aga Khan University Hospital, Karachi.

³ Department of Gastroenterologist, Doctors Hospital, Peshawar.

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Correspondence: Prof. Dr. Javed Iqbal Farooqi, Chairman Experts Meeting, Bhurban, Pakistan.

E-mail: dr_farooqi@hotmail.com

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INTRODUCTION

Gastroesophageal variceal bleeding is a major complication of portal hypertension (HTN) resulting from cirrhosis. It occurs in 25 - 35% of patients with cirrhosis and accounts for 80 - 90% bleeding episodes in these patients.¹⁻³ Variceal bleeding is associated with greater morbidity and mortality than other causes of gastrointestinal bleeding, as well as higher economic burden.⁴⁻⁶ Upto 30% of initial bleeding episodes are fatal and as many as 70% 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%.^{7,8}

There have been numerous advances in the management of variceal bleeding in patients with cirrhosis. Many milestones, review articles and guidelines including UK Guidelines,⁹ OMGE Guidelines,¹⁰ AASLD,¹¹ Baveno,¹² PSG Guidelines-2006,¹³ etc., have been published to suggest the evidence-based appropriate management of patients with variceal bleeding.

Gastroenterologists/Hepatologists face some unique challenges in Pakistan regarding the management of variceal bleeding. Prevalence of hepatitis and liver cirrhosis and its associated complications are still on rise. There seems to be a major chunk of unrecognized

cases of liver cirrhosis in the community. Access to health care is only patchy and very limited. There is lack of adequate diagnostic facilities including endoscopic equipment, and moreover cost of accessories and maintenance costs are extremely high. There is a lack of human resource (HR), capable of recognizing the severity of the problem and risk stratification - which determines the referral pattern. There is a lack of applicability of the current prognostic systems and development of new systems. The availability and safety of blood products is questionable. Training slots are deficient for healthcare workers. Awareness of general principles of resuscitation with a local twist to these is highly needed. Issues are being encountered with Sengstaken-Blakemore tube. Patient's attitude towards specialized care is a hurdle in delivering the best treatment. There is a lack of affordability on patients' part. Issues are encountered regarding more definitive therapies for cirrhotic patients including liver transplant (LT) and transvenous intrahepatic portosystemic shunt (TIPSS).

Keeping in view these challenges, limited resources and multifaceted healthcare system, there is an utmost need to develop clinical practice guidelines (CPGs) to provide a data-supported approach to the management of patients with varices and variceal hemorrhage in Pakistan.

Management of ectopic varices, Portal Hypertensive Gastropathy (PHG) and Gastric Antral Vascular Ectasia (GAVE) are beyond the scope of these guidelines as these are focusing on esophageal and gastric varices and not all bleedings related to portal hypertension.

METHODOLOGY

Eminent experts from all over the country kindly consented to attend the meeting to develop Clinical Practice Guidelines (CPGs) with aims to define key events in variceal bleeding, to review the existing evidence on the natural history, the diagnosis and the therapeutic modalities of variceal bleeding, and to make evidence-based recommendations for the management of patients with variceal bleeding in Pakistan. Three working committees were made in advance to review literature and make guidelines on the pre-primary and primary prophylaxis of variceal bleeding, management of acute variceal bleeding, and secondary prophylaxis of variceal bleeding. All the experts agreed upon to adopt Oxford System of Grading of Evidence and Recommendations¹³ for drafting these CPGs.

In September 2013, all the relevant global and local literature including review articles, guidelines, statements and original research data were reviewed in a meeting to draft these CPGs. The available evidence was graded according to the criteria given in Table I. All recommendations for clinical practice were graded

according to the criteria given in Table II. After the meeting, the final draft was sent to all the members for final review and approval.

Objectives of the guidelines: These guidelines were formulated to 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.

Target population: These guidelines are applicable to patients of liver cirrhosis with portal hypertension with or without esophageal and/or gastric varices.

Target users: These guidelines are developed for all segments of healthcare involved in the evaluation and management of cases with variceal bleeding, including hospitals, all levels of healthcare providers, i.e. primary level - individuals and facilities, secondary level - regional hospitals with and without endoscopy facilities and other support facilities, tertiary level - having endoscopic facility, intensive care facility, hepatobiliary surgery, and transplant facility, etc.; policy makers/administrators, and patients.

DISCUSSION

Portal hypertension: Portal hypertension is a progressive complication of cirrhosis, regardless of its etiology. Portal hypertension results from the combination of increased intra-hepatic vascular resistance and increased blood flow through the portal venous system.¹⁵⁻¹⁷

Hepatic Venous Pressure Gradient (HVPG), which is the difference between the wedged (or occluded) hepatic venous pressure and the free hepatic venous pressure, is a fair estimate of portal hypertension.¹⁸ Normal HVPG is 3 - 5 mmHg. Portal HTN is defined as HVPG of more than 5 mmHg. Clinically significant portal hypertension is defined as HVPG of 10 mmHg or more.¹⁹

Natural history of varices: Patients with liver cirrhosis and portal hypertension develop two types of varices depending upon the site of occurrence: esophageal varices and/or gastric varices.

When cirrhosis is first diagnosed, esophageal varices are present in ~40% of compensated and 60% of decompensated patients.²⁰ In cirrhotic patients without varices at first endoscopy, the rate of development is approximately 8% per year.²¹ In patients with evidence of varices, progression from small varices to medium or large varices occurs at an average rate of 8 % per year (5 - 12% at 1 year and 31% at 3 years).²² The rate of progression may be higher (22 vs. 2%) in the presence of any of the following factors: higher Child-Pugh-Turcotte (CTP) class, alcohol-related cirrhosis, and high-risk stigmata of bleed (e.g., red wale marks).²¹ The annual risk of bleeding from esophageal varices is

5 - 15% depending on the size of varices. Bleeding risk is higher among persons with small varices, as compared with persons without varices (12 vs. 2%).²¹ The highest annual risk of bleeding within the first year

occurs in persons with large varices.²³ The predictors of bleeding include presence of decompensated cirrhosis (CTP class B or C), size of varices, and presence of high-risk stigmata upon endoscopy (red wale

Table I: Oxford centre for evidence-based medicine levels of evidence.

Level	Therapy / prevention, aetiology / harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs.	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations.	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres.	SR (with homogeneity*) of prospective cohort studies.	SR (with homogeneity*) of Level 1 economic studies.
1b	Individual RCT (with narrow Confidence Interval‡).	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population.	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre.	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses.
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series.	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies.	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs.	SR (with homogeneity*) of Level >2 diagnostic studies.	SR (with homogeneity*) of 2b and better studies.	SR (with homogeneity*) of Level >2 economic studies.
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up).	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on split-sample§§§ only.	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases.	Retrospective cohort study, or poor follow-up.	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses.
2c	"Outcomes" Research; Ecological studies.	"Outcomes" Research		Ecological studies.	Audit or outcomes research.
3a	SR (with homogeneity*) of case-control studies.		SR (with homogeneity*) of 3b and better studies.	SR (with homogeneity*) of 3b and better studies.	SR (with homogeneity*) of 3b and better studies.
3b	Individual case-control study.		Non-consecutive study; or without consistently applied reference standards.	Non-consecutive cohort study, or very limited population.	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§).	Case-series (and poor quality prognostic cohort studies***).	Case-control study, poor or non-independent reference standard.	Case-series or superseded reference standards.	Analysis with no sensitivity analysis.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Notes:

- * By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
- † Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
- ‡ See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
- § Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
- §§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
- §§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
- †† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
- ‡‡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
- ††† Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
- †††† Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
- ** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
- *** By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
- **** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic).

marks/cherry red spots).²⁴ The 1-year rate of recurrent variceal hemorrhage is approximately 60%.²⁵ The 6-week mortality with each episode of variceal hemorrhage is approximately 15 - 20%.²⁶

Table II: Grades of recommendation.

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies.
C	Level 4 studies or extrapolations from level 2 or 3 studies.
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

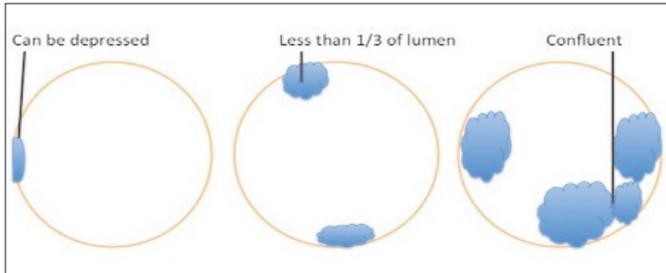


Figure 1: Classification of esophageal varices.

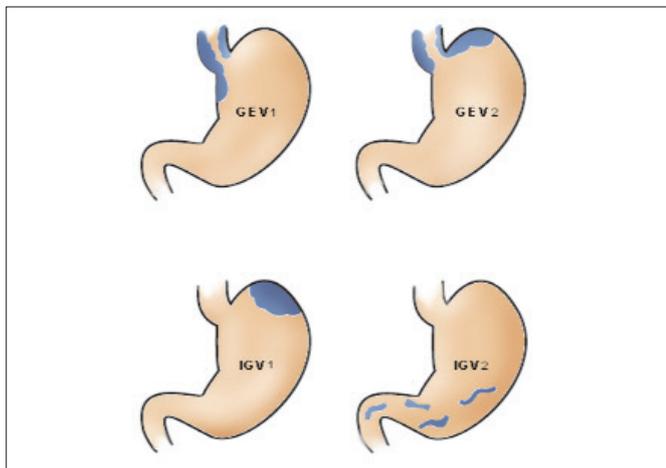


Figure 2: Sarin's classification of gastric varices.

GEV1 = Gastro-Esophageal Varix 1
 GEV2 = Gastro-Esophageal Varix 2
 IGV1 = Isolated-Gastric Varix 1
 IGV2 = Isolated-Gastric Varix 2

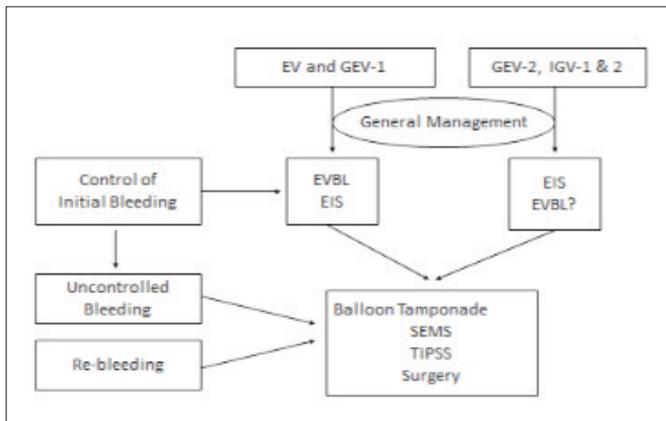


Figure 3: Management of acute variceal bleeding.

Gastric varices are less prevalent than esophageal varices, and account for approximately 20 - 30% of cases of variceal bleeding. The prevalence of gastric varices in patients with portal hypertension varies from 6 - 78% and approximately 25% of gastric varices bleed during lifetime, with a higher bleeding incidence for fundal varices.²⁷ Gastric varices occur five times more often in patients with esophageal varices that have previously bled than in those that have never bled. Although gastric variceal haemorrhage occurs less frequently than esophageal variceal haemorrhage, the severity of bleeding and mortality, especially with fundal varices, is greater. Risk factors for gastric variceal haemorrhage include the size of fundal varices-large, medium, small (defined as 10 mm, 5 - 10 mm, and < 5 mm, respectively), CTP class (C,B,A), and endoscopic presence of variceal red spots (defined as localized reddish mucosal area or spots on the mucosal surface of a varix).²⁸

Classification of varices: Esophageal varices are classified into small, medium and large esophageal varices¹ as detailed below (Figure 1):

Small varices generally defined as minimally elevated veins above the esophageal mucosal surface, medium varices defined as tortuous veins occupying less than one-third of the esophageal lumen, and large varices defined as those occupying more than one-third of the esophageal lumen.

Gastric varices are classified into: 1) Primary and secondary gastric varices according to timing of appearance; and (2) Gastroesophageal Varices (GEV) - 1 and 2, and Isolated Gastric Varices (IGV) - 1 and 2, according to their relationship with esophageal varices and their location in the stomach (Figure 2).²⁶ Primary gastric varices are those detected at the time of the first endoscopy, whereas secondary gastric varices are those which occur within two years of eradication of esophageal varices.

Gastroesophageal varices-1 are those which are connected with esophageal varices and are located on the lesser curvature.

Gastroesophageal varices-2 are those which are connected with esophageal varices and are located in the fundus.

Isolated gastric varices-1 are those which are not connected with esophageal varices and are located in the fundus.

Isolated gastric varices-2 are those which are located in the stomach outside the fundus and even in the first part of duodenum.

Screening for varices: There are two ways to screen for varices including upper Gastrointestinal (GI) endoscopy and non-endoscopic parameters.

Many studies suggest that all patients should undergo an screening upper GI endoscopy at the time of initial diagnosis of cirrhosis for esophageal and gastric varices.^{22,23} As mentioned before, Pakistan has restricted resources and most patients are poor; therefore, at present it cannot be made mandatory for all patients to undergo screening upper GI endoscopy at the time of diagnosis of cirrhosis.

Non-endoscopic parameters include platelets count, presence of splenomegaly, ratio of platelets count and splenomegaly, increased portal vein diameter > 13 mm, and more recently Transient Elastography (TE) by Fibroscan. All of these have been suggested to be useful in selecting patients with a high risk of having large esophageal varices. However, absence of these tests, alone or in combination, is not accurate enough to completely discard the presence of esophageal varices.^{23,29,30} Abbasi *et al.* found in their observational study that platelet count was significantly and inversely correlated with the grade of esophageal varices.³¹ Recently Sharma *et al.* found that measurement of spleen stiffness can differentiate large vs. small varices and non-bleeder versus bleeder.³² However, all these non-endoscopic parameters need to be evaluated further by local studies.

Recommendations:

1. Ideally, all patients should undergo screening upper GI endoscopy at the time of initial diagnosis of cirrhosis for varices (1a; A).
2. If patient have no varices, repeat endoscopy should be done: (a) Every 2, years in case of compensated cirrhosis (5; D); (b) Annual, in case of decompensated cirrhosis (5; D).
3. HVPG needs further study to select patients for different therapies (5; D)

Pre-primary prophylaxis of varices: Pre-primary prophylaxis means prevention of the development of varices. In patients who do not have gastroesophageal varices, there has been no difference between placebo and β -blockers (BB) in the prevention of development of varices. Serious adverse events were more common among patients in the β -blockers group.³³ Therefore, treatment with non-selective β -blockers (NSBB) is not recommended in this setting. The main focus at this stage is to treat the underlying cause of cirrhosis which will reduce portal hypertension and may prevent the development of clinical complications.^{23,34} This includes abstinence in alcoholics, anti-viral in viral cirrhosis, lifestyle changes in non-alcoholic steatohepatitis (NASH), corticosteroids in autoimmune hepatitis, phlebotomies in hemochromatosis, copper chelating agents in Wilson's disease and use of ursodeoxycholic acid (UDA) in primary biliary cirrhosis. Surveillance endoscopies should be performed every 2 years in these

patients; and annually, if decompensation occurs.³⁵ HVPG measurement needs further studies to select treatment in patients without varices.

Recommendations:

1. Treatment of the underlying cause of cirrhosis should be undertaken to prevent the development of portal hypertension or reduce already developed portal hypertension in an attempt to prevent the development of varices (1a; A).
2. At present, β -blockers are not recommended to be used in pre-primary prophylaxis of varices (1b; A).

Primary prophylaxis of varices: In chronic liver disease, 30 - 50% of patients with portal hypertension will bleed from varices and about 50% will die from the effects of the first bleed.^{24,36-39} Thus, to prevent the first episode of bleeding seems essential. Non-selective β -blockers with or without nitrates and endoscopic variceal band ligation (EVBL) have been used for the primary prophylaxis of variceal bleeding.^{22,40}

Patient with cirrhosis and small Esophageal varices:

Small esophageal varices are of two types:

1. Low-risk small esophageal varices; (a) Small esophageal varices in cirrhosis CTP class A; (b) Small esophageal varices in cirrhosis CTP class B or C, but without any red wale marks or cherry red spots.
2. High-risk small esophageal varices: (a) Small esophageal varices in cirrhosis CTP class A, and having red wale marks or cherry red spots; (b) Small esophageal varices in cirrhosis CTP class B or C

A large multicenter, placebo-controlled trial reported that patients with small varices treated with Nadolol had a significantly slower progression to large varices (11% at 3 years) than patients who were randomized to placebo (37% at 3 years), with no differences in survival.⁴¹ In patients with low risk small esophageal varices, long-term benefits of the use of non-selective β -blockers (NSBB) are not well established. In patients with high risk small esophageal varices, treatment with non-selective β -blockers is strongly recommended.²³ However, patients who are not candidates for non-selective β -blockers therapy, surveillance endoscopy is recommended every two years and annually in those with hepatic decompensation.²² HVPG, wherever available, can be utilized to stratify patients as responders and non-responders in a single procedure using intravenous Propranolol to reduce or abolish the risk of first variceal bleed. A meta-analysis of 10 randomized controlled trials evaluating isosorbide mononitrate (ISMN) alone or with non-selective β -blockers showed no beneficial effects in the primary prophylaxis of esophageal varices.⁴² EVBL is not recommended for the primary prophylaxis of small varices.³⁵

Recommendations:

1. In high-risk small esophageal varices, NSBB should be used. In low-risk small esophageal varices, NSBB may be used if desired by the treating physician. Nitrates alone or in combination with NSBB not recommended (1b;A)
2. EVBL is not recommended in the primary prophylaxis of small esophageal varices (5; D).
3. Repeat endoscopy should be done: (a) Every two years in case of compensated cirrhosis (III;C); (b) Annual in case of decompensated cirrhosis (III;C)

Patients with cirrhosis and medium or large esophageal varices: Primary prophylaxis with non-selective β -blockers and endoscopic variceal band ligation (EVBL) has been shown independently to decrease the risk of a first episode of variceal bleeding.^{20,43} A systematic review of 19 randomized trials found a beneficial effect of band ligation on primary prevention of upper gastrointestinal bleeding in patient with esophageal varices.⁴⁴ A meta-analysis of 12 randomized controlled trials evaluating the role of non-selective β -blockers and EVBL detected no significant difference in the incidence of gastrointestinal bleeding (EVBL 16.37% versus β -blockers 20.50%; RR 0.79 [95% CI 0.61 to 1.02]; RR reduction -21% [95% CI -39% to 2%]; $p=0.07$), showing that EVBL and β -blockers therapy were equally effective in the primary prevention of bleeding.⁴⁵ Three randomized controlled trials have investigated the efficacy of propranolol and EVBL in patients with high-risk esophageal varices. In these studies EVBL of the varices is safe and more effective than propranolol for the primary prevention of variceal bleeding, but not mortality.⁴⁶⁻⁴⁸ For EVBL in primary prophylaxis, recommended intervals between two sessions should be 2-4 weeks.⁴⁹ Endoscopic injection sclerotherapy (EIS), TIPSS and shunt surgery have not been advocated for primary prophylaxis so far.

Choice of non-selective β -blockers in primary prophylaxis: Propranolol, nadolol and more recently, carvedilol have been extensively studied for use as primary prophylaxis of gastro-esophageal variceal hemorrhage. For effective β -blockade, dose should be adjusted to the maximal tolerated dose (25% reduction in heart rate from baseline or heart rate upto 55 beats/minute or systolic blood pressure upto 90 mmHg). However, this does not establish responder or non-responder status of the patient. The adverse reactions reported with non-selective β -blockers are shortness of breath, nausea, vomiting, hypotension, and impotence. Twenty-five percent of the patients have contraindications to β -blockers and discontinuation rate is ~15% of patients. Two studies investigated the role of carvedilol in the primary prophylaxis as compared to propranolol and EVBL, both studies showed that carvedilol is an effective and better option for primary

prophylaxis in patients with high-risk esophageal varices and it is found to be superior in achieving an adequate HVPG response (a HVPG reduction of $\geq 20\%$ of baseline or ≤ 12 mmHg) as compared to propranolol.^{50, 51} In a recent study from Karachi, carvedilol was found to be as effective as EVBL for the prevention of first variceal bleed in cirrhotic patients with no difference in mortality between groups. Non-selective β -blockers should be continued indefinitely.⁵²

Recommendations:

1. Primary Prophylaxis must be given in the form of NSBB or EVBL (1a; A); (a) Choice of treatment should be based on local resources and expertise, physician/patient preference and side effects, and contra-indications (5; D); (b) Carvedilol is an emerging and effective alternative β -blocker (1b; A); (c) Nitrates alone or with β -blockers should not be used for primary prophylaxis of variceal bleeding (1a; A).
2. There is no role of EIS, TIPSS and/or Shunt Surgery (1a; A)

Primary prophylaxis of gastric varices: Data on prevention of the first bleeding in patients with gastric varices is sparse. It is conceivable that beta-blocker therapy is equally effective in this situation. The efficacy of cyanoacrylate in these patients remains controversial.⁵³

Management of acute variceal bleeding: Variceal haemorrhage is typically an acute clinical event, characterized by severe gastrointestinal bleeding presenting as hematemesis with or without melena or hemochezia. 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 haemorrhage, 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: esophageal varices or gastric varices.

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 widely used in clinical practice. Therefore, short of endoscopy, detailed history and good physical examination remain

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.

Signs of liver cirrhosis and/or portal hypertension are present.

Definitions in the context of acute variceal bleeding:

The committee adopted the following definitions in the context of acute 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

Timeframe of acute bleeding: Acute bleeding is represented by an interval of 120 hours (5 days) from time zero.¹² 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 timeframes.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 /minute from baseline pulse rate.

After six hours: Any of the following factors:

Occurrence of haematemesis from the 6-hour point.

Reduction in blood pressure of more than 20 mm Hg from the 6-hours point.

Increase in pulse rate of more than 20 beats per minute from the 6-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 to above 27% or hemoglobin to above 9 g/dl.

Failure: Signifies need to change therapy; any of the following criteria defines failure, whichever occurs first:¹¹

Fresh hematemesis > 2 hours 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 hemoglobin (≈9% drop in Ht) if no transfusion is administered.

Death.

Adjusted Blood Transfusion Requirement Index (ABRI) > 0.75 at any time point.

$$ABRI = \frac{\text{Blood units transfused}}{(\text{Final Hematocrit} - \text{Initial Hematocrit})} + 0.1$$

Hematocrit (or Hemoglobin) is measured at least every 6 hours for the first 2 days, and then every 12 hours for days 3 - 5.

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.¹²

Early mortality: Death within 6 weeks of the initial episode of bleeding.⁹

Treatment of acute variceal bleeding: Ideally, the 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. Therapy is aimed at correcting hypovolemic shock and at achieving hemostasis at the bleeding site. Proper management of such patients include: initial assessment, resuscitation, blood volume replacement, vasoactive agents, prevention of associated complications such as bacterial infections, hepatic encephalopathy, coagulopathy and thrombocytopenia, and specific therapy.

Initial assessment: History and physical examination has pivotal role. On arrival of the patient, baseline investigations must be sent to laboratory. These must include Complete Blood Count (CBC), platelets count, Prothrombin Time (PT), Liver Function Tests (LFTs), urea and creatinine, serum electrolytes, glucose, blood grouping and cross matching. Child-Turcotte-Pugh (CTP) score should be calculated to classify the patient accordingly. Additional tests to determine comorbidity and prognosis include abdominal ultrasound (preferably bedside, so shifting of the patient to radiology department is not required), ECG in patients over > 45 years of age, and O₂ saturation.

Resuscitation of the patient: The most important step in the management of variceal bleeding is to evaluate the patient hemodynamically. If in shock, basic ABC (passing airway, ensuring good breathing, and maintaining circulation - pulse and blood pressure) needs to be achieved before doing anything else. Adequate resuscitation is achieved with pulse less than 100 per minute, systolic blood pressure more than 100 mm Hg, no postural drop, and O₂ saturation more than 90%. At least 2 wide bore (16 G preferably) IV cannulae should be passed and ideally 4 - 6 units of blood should be arranged. Acute variceal bleeding is a medical emergency that should be managed under intensive care facilities by a team of experienced medical staff including endoscopists, hepatologists, surgeons and nurses. Minimum facilities in the unit should include cardiac monitoring, ventilation, pulse oximetry and infusion pumps. Endotracheal Tube (ET) intubation may be considered in a patient if in shock, mental status change, continuous heavy bleeding, and respiratory compromise. Nasogastric (NG) tube may be placed in selected patients with active bleeding for clearing the field of vision and monitoring of continuous bleeding. Balloon tamponade should only be used as a temporary bridge by trained personnel until definitive treatment can be instituted, for a maximum of 24 hours, and preferably in an intensive care facility. It should be used in case of massive bleeding, failure of therapy with active bleeding and hemodynamic instability despite adequate pharmacotherapy and endoscopic therapy.

Blood volume replacement: Blood volume restitution should be done cautiously and conservatively, using plasma expanders to maintain hemodynamic stability and packed red blood cells to maintain the hemoglobin at approximately 7-8 g/dl, depending on other factors such as patient's co-morbidities, age, hemodynamic status and presence of ongoing bleeding clinically. Colloids may be used cautiously while awaiting availability of blood and blood products. Over transfusion should be avoided as this can increase portal pressures and exacerbate further bleeding.

Vasoactive drugs: These are used to arrest bleeding by decreasing pressure and blood flow within the esophageal varices, thus, allowing hemostasis at the bleeding points. Vasoactive drugs have been shown to control acute variceal bleeding in about 80% of patients.⁵⁴⁻⁶⁰ Vasoactive therapy can be used empirically when variceal bleeding seems likely on clinical grounds. The current recommendation is to start a vasoactive agent as early as possible from the time of admission or even upon the patient's transfer to the hospital.^{54,55} The agents available are: Vasopressin (\pm Nitroglycerine) or its analogue - Terlipressin, and Somatostatin or its analogues - Octreotide and Vapreotide.

Vasopressin was the first vasoactive agent used in the treatment of acute variceal bleeding. It has, however,

significant systemic side-effects which include myocardial and mesenteric ischemia and infarction.⁶¹ The addition of Nitroglycerine to Vasopressin-enhances its efficacy and reduces the cardiovascular side-effects.^{62,63}

Terlipressin, a synthetic vasopressin analogue with fewer side-effects and a longer half-life than vasopressin, is effective in controlling acute variceal bleeding.^{64,65} Terlipressin is administered as intravenous (IV) injections of 2 mg bolus and 1 mg every 4 - 6 hours for 2-5 days. A meta-analysis demonstrated that Terlipressin was associated with a 34% relative risk reduction in mortality compared to placebo.⁶⁴

Somatostatin and its synthetic analogues, Octreotide and Vapreotide, control acute variceal bleeding in upto 80% of patients and are generally considered to be equivalent to Terlipressin but superior to Vasopressin for the control of acute variceal haemorrhage.⁶⁴ Somatostatin is given as an IV 250 mcg bolus followed by 250 mcg/hour infusion. Octreotide is administered as a bolus injection of 100 mcg followed by an infusion at a rate of 25 - 50 mcg/hour. Somatostatin or Octreotide therapy should be maintained for 5 days to prevent early rebleeding.

In acute variceal bleeding, Terlipressin may have an added advantage as it can potentially reverse hepatorenal syndrome.⁶⁶ In addition, Terlipressin has been shown to have a more sustained hemodynamic effect compared to treatment with Octreotide.⁶⁷ Octreotide and Terlipressin have been found to have similar control of initial bleeding and similar risk of rebleeding.⁶⁸ Regarding duration of Terlipressin therapy, 24 hours has been found to be as effective as 72 hours, when it is used in conjunction with EVBL.⁶⁹

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

Bacterial infections: Bacterial infections are seen in about 20% of cirrhotics presenting with upper gastrointestinal bleeding within 48 hours.^{70,71} The incidence of sepsis increases to almost 66% at two weeks.⁷²⁻⁷⁷ Development of bacterial infection is associated with high mortality and variceal re-bleeding.^{71,75} Antibiotic prophylaxis has been shown to reduce the rate of infection, spontaneous bacterial peritonitis and rebleeding.⁷⁶⁻⁸⁰ In addition, antibiotic prophylaxis was clearly proven in a meta-analysis to significantly increase the survival rate.⁸¹ Short-term antibiotic prophylaxis for 7 days should be considered the standard of care in cirrhotic patients with upper gastrointestinal bleeding, irrespective of the type of haemorrhage (variceal or non-variceal) or the presence or absence of ascites. Either intravenous third generation cephalosporins (Ceftriaxone) or oral quinolones (Ciprofloxacin) are generally recommended.

Hepatic encephalopathy: In patients who present with or develop encephalopathy, this should be treated with Lactulose or other drugs. 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.

Coagulopathy and thrombocytopenia: Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data, but it may be considered if a platelets count is less than 50,000/cmm.

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. Endoscopic therapy depends upon the source of bleeding.

Esophageal varices: Endoscopic therapy includes Endoscopic Injection Sclerotherapy (EIS) and Endoscopic Variceal Band Ligation (EVBL). EIS stops bleeding in 80-90% of patients with acute variceal haemorrhage.⁸²⁻⁸⁴ EVBL is more effective than EIS in controlling acute esophageal variceal bleeding, is associated with fewer complications and a survival advantage.⁸⁵⁻⁸⁸ Technically, EVBL may be difficult at times because of limited visualization from bleeding and EIS is used as it is easier to perform in this setting. Administering vasoactive agents before endoscopic therapy, facilitates endoscopy, improves control of bleeding, transfusion requirements, and reduces 5-day re-bleeding rate,⁸⁹⁻⁹² but with no effect on mortality,⁹³ both in low-risk and high-risk patients,⁹⁴ and even if administered just after the endoscopic procedure.⁹⁵⁻⁹⁷

Gastric varices: Endoscopic therapy depends upon the type of gastric varices. GEV1 are treated as esophageal varices. GEV2 and IGVs are treated with Injection of Cyanoacrylate glue, which controls acute gastric bleeding in 90% cases,⁹⁸⁻¹⁰⁰ better than alcohol and band ligation.^{101,102} Histoacryl should be mixed with Lipiodol in a ratio of 0.5:0.8 ml. After ensuring intravariceal position of the needle, Histoacryl should be injected in a slow and controlled fashion and should not exceed 1 ml at any one site as there is a risk of thrombotic complications including pulmonary embolism. Histoacryl injection sclerotherapy must only be performed by experienced endoscopist.

Balloon-occluded retrograde transvenous obliteration (BRTO) has been introduced as a new method to treat GV. BRTO, and is also effective and has the potential benefit of increasing portal hepatic blood flow and, therefore, may be an alternative for patients who may not tolerate TIPS. However, BRTO obliterates spontaneous portosystemic shunts, potentially aggravating portal

hypertension and its related complications. The role of BRTO in the management of acute GV bleeding is promising but it merits further evaluation.¹⁰³

Patients in CTP class C without active bleeding, and CTP class B with active bleeding at presentation, after securing hemostasis with pharmacological and endoscopic therapy, are at high-risk of rebleeding; therefore, in these patients an early TIPS within 72 hours (ideally ≤ 24 hours) has been found to improve survival significantly.^{104,105}

Treatment failures: Treatment failures may be of two types: Rebleeding during the first 5 days may be managed by a second attempt at endoscopic therapy. If rebleeding is severe, PTFE-covered TIPS is likely the best option.¹⁰⁶

Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by TIPS with PTFE-covered stents.^{107,108} 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).¹⁰⁹ Uncontrolled data suggest that self-expanding covered esophageal metal stents may be an option in refractory esophageal variceal bleeding, although further evaluation is needed.¹¹⁰⁻¹¹² Emergency surgical portocaval shunt (within 8 hours of onset of bleeding) has been reported to be associated with almost universal control of bleeding and a low mortality over a 30-year period, further validation is also needed here.¹¹³

Recommendations:

1. Resuscitation: (a) ICU management is recommended (2;C); (b) ET intubation may be considered in a patient if in shock, mental status change, continuous heavy bleeding, and respiratory compromise (5;D); (c) NG tube may be placed in selected patients with active bleeding for clearing the field of vision and monitoring of continuous bleeding (5;D); (d) Balloon tamponade should only be used as a temporary bridge by trained personnel until definitive treatment can be instituted, for a maximum of 24 hours, and preferably in an intensive care facility (5;D).

2. Blood volume replacement: (a) Blood volume restitution should be done cautiously and conservatively, using plasma expanders to maintain hemodynamic stability and packed red blood cells to maintain the hemoglobin at approximately 7 - 8 g/dl, depending on other factors such as patient's co-morbidities, age, hemodynamic status and presence of ongoing bleeding clinically (1b;A); (b) Colloids may be used cautiously while awaiting availability of blood and blood products (5; D).

3. Vasoactive therapy: (a) In suspected variceal bleeding, vasoactive drugs should be started as soon as

possible, before endoscopy (1b; A); (b) The efficacy of Terlipressin is equal to Octreotide as an adjunct therapy for the control of esophageal variceal bleed and in-hospital survival (1b; A); (c) In patients with esophageal variceal bleeding, a 24-h course of Terlipressin is as effective as a 72-h course when used as an adjunctive therapy to successful EVBL (1b; A); (d) 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 (1c; A); (e) At the primary care level, pharmacological therapy should be started at the time of initial contact with the patient (1c; A).

4. Bacterial infections: (a) Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted from admission (1a; A); (b) Intravenous Ceftriaxone / Oral quinolones are recommended for most patients (1b; A); (c) Intravenous Ceftriaxone is preferable in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis (5; D).

5. Hepatic encephalopathy: (a) Recommendations regarding management and prevention of encephalopathy in patients with cirrhosis and upper GI bleeding cannot be made on the basis of currently available data (5;D); (b) It is best left to the choice of caring physician (5; D).

6. Coagulopathy and thrombocytopenia: (a) Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data; anyhow, it may be considered if a platelet count is less than 50,000 /cmm (5; D); (b) PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis (1b; A).

7. Specific therapy: (a) Patients with GI bleeding and features suggesting cirrhosis should have upper endoscopy as soon as possible after admission (within 12 h) after hemodynamic stabilization with airway control (5-D); (b) Endoscopic therapy is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause of bleeding (1a;A); (c) Endoscopic Variceal Band Ligation (EVBL) 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 (1b;A); (d) Endoscopic Injection Sclerotherapy (EIS) with tissue adhesive (e.g. N-butyl-cyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) (1b;A) and those gastro-esophageal varices type 2 (GEV2) that extend beyond the cardia (5;D); (e) EVBL or EIS with tissue adhesive can be used in bleeding from

gastroesophageal varices type 1 (GEV1) (4;C); (f) Combination of pharmacological therapy and endoscopic therapy is the most rational approach in the treatment of acute variceal haemorrhage. (1;a A)

8. Early TIPSS: (a) An early TIPSS within 72 h (ideally 24 h) should be considered in patients at high-risk of treatment failure (e.g. CTP class C <14 points or CTP class B , or with active bleeding) after initial pharmacological and endoscopic therapy (1b;A); (b) HVPG measurements may be helpful to select patients for early TIPS

9. Treatment failures: (a) Refractory Bleeding - Persistent bleeding despite combined pharmacological and endoscopic therapy; (i) It is best managed by TIPS with PTFE-covered stents (1b;A); (ii) Balloon tamponade should only be used in massive bleeding as a temporary "bridge" until definitive treatment can be instituted (for a maximum of 24 h, preferably in an intensive care facility); (iii) Surgery may be considered in the absence of facilities for TIPS in selected patients (child A Cirrhosis with acute, uncontrolled variceal bleeding (5-D); (iv) Emergency surgical portocaval shunt (within 8 hours of onset of bleeding) has been reported to be associated with almost universal control of bleeding and a low mortality over a 30-year period (5-D); (v) Uncontrolled data suggest that self-expanding covered esophageal metal stents may be an option in refractory esophageal variceal bleeding, although further evaluation is needed (4;C); (b) Re-bleeding during the first 5 days: (i) It may be managed by a second attempt at endoscopic therapy (2b;B); (ii) If re-bleeding is severe, PTFE-covered TIPSS is likely the best option (2b;B)

Secondary prophylaxis of varices: Secondary prophylaxis is the prevention of recurrent bleeding after a first episode variceal bleed. All those patients, who survive an episode of acute variceal bleed, have a high risk of rebleeding. About 60% will rebleed within 2 years with a mortality of 33%.^{95,25} Therefore, it is mandatory that after successful recovery from acute variceal bleeding episode, all patients must be started on therapy to prevent recurrence of bleeding prior to discharge from the hospital.^{22,114} Patients who require shunt surgery/ TIPSS to control the acute episode, do not require further preventive measures. All these patients should be referred to a transplant center, if they are otherwise a candidate (i.e., CTP score ≥ 7 or a MELD score ≥ 15).

Definitions in the context of secondary prophylaxis: The committee adopted following definitions of key events in the context of secondary prophylaxis:

Timing: It should be started as soon as possible from day 6 of the index variceal bleeding episode or at the time of discharge. The time of start of secondary prophylaxis should be documented.

Failure to prevent re-bleeding is defined as a single

episode of clinically significant re-bleeding from portal hypertensive sources after day 5.

Clinical significant re-bleeding is defined as recurrent melena or hematemesis, resulting in any of the following: hospital admission, blood transfusion, 3 g drop in Hb, and death within 6 weeks.

Treatment modalities: Various modalities used for secondary prophylaxis include pharmacological therapy, endoscopic therapy with or without pharmacological therapy, and TIPSS.

Pharmacological therapy: Secondary prophylactic therapy with pharmacological therapy is based on the assumption that a sustained reduction in portal pressure reduces the incidence of variceal rebleeding. Non-selective Beta Blockers (NSBB) with or without Isosorbide Mononitrate (IM) have been widely studied in the secondary prophylaxis of variceal bleeding.

Non-selective beta blockers monotherapy: NSBBs are still the mainstay of pharmacotherapy.¹¹⁵⁻¹¹⁷ A meta-analysis of 12 randomized controlled trials comparing NSBB to either no treatment or placebo, showed a statistically significant reduction in the risk of recurrent bleeding and survival advantage.¹¹⁸ The incidence of recurrent variceal bleeding was 42.7% in the placebo group and 32% in the beta-blocker group, a reduction in the risk of bleeding by one third, and mortality from 27% to 20%.^{95,119}

Non-selective Beta Blockers (NSBBs) treatment in cirrhotic patients is an undisputed strategy for bleeding prophylaxis. Nevertheless, recent studies question the efficacy and safety of NSBBs in patient with advanced cirrhosis, particularly in case of refractory ascites and spontaneous bacterial peritonitis. According to a window hypothesis,¹²⁰ NSBBs are beneficial only in decompensated patients with medium-large varices but not in patients with early or end-stage cirrhosis with refractory ascites. Data from a study performed by Serstè *et al.*¹²¹ showed that mortality in patients with refractory ascites was increased if taking NSBBs. The same group hypothesized that β -blockade could induce counter-regulatory over-activation of the Renin-Angiotensin Aldosterone axis, increasing incidence of paracentesis-induced circulatory dysfunction, which could be associated with impaired renal function and reduced survival.¹²² These data were not confirmed by another study on patients with ascites taking propranolol,¹²³ moreover, by analyzing all published randomized controlled trials on prophylaxis for variceal hemorrhage, bleeding unrelated mortality was similar between patients on NSBBs and those treated with other therapies in primary (277/955 vs. 287/1175; OR 0.91 95% CI 0.73 - 1.15) and secondary prophylaxis (188/1143 vs. 225/1208; OR 0.87 95% CI 0.68 - 1.12) without heterogeneity amongst studies, while causes of death were not different between patients on and off

NSBBs therapy. These results were confirmed in the subgroup analysis of studies with higher prevalence of ascites (> 50%).¹²⁴ While a beneficial role of NSBB on several outcomes in cirrhotic patients is well established, the effect in patients with refractory ascites is still unclear, and a possible harmful effect is under debate. A potential harmful effect of propranolol in patients with cirrhosis with refractory ascites deserves further confirmation.

Non-selective beta blockers with isosorbide mononitrate: Further reduction in portal pressure can be achieved by adding ISMN.¹²⁵ Some early RCTs and systematic reviews suggested greater reduction in rebleeding rates with combination pharmacological therapy as compared to BB alone,^{25,95,119} strengthening the impression that combination of BB and ISMN is the therapy of choice in secondary prophylaxis. However, according to local data and a recent meta-analysis, the combination of NSBB and ISMN is not different from NSBB alone regarding the rate of overall re-bleeding or mortality, but has a higher rate of side-effects.^{126,127}

Endoscopic therapy: Two types of endoscopic therapies have been used in the secondary prophylaxis of variceal bleeding: Endoscopic Injection Sclerotherapy (EIS) and Endoscopic Variceal Band Ligation (EVBL). The latter has almost replaced the former one.

Endoscopic injection sclerotherapy: It is performed every 10 - 14 days until the varices are obliterated, which typically requires 5 or 6 sessions. Sclerotherapy decreases rebleeding rates and mortality as compared to placebo,¹²⁸ but is associated with serious complications (e.g., esophageal strictures, bleeding from ulcers).

Endoscopic variceal band ligation: Sclerotherapy has been replaced by EVBL, since it has significantly better outcomes (rebleeding, mortality and side-effects) compared with sclerotherapy.¹²⁹⁻¹³³ Similar to sclerotherapy, EVBL is performed every 10 - 14 days until the varices are eradicated, which usually takes 3 or 4 sessions.

Combination of EIS and EVBL: The addition of sclerotherapy to ligation has not been shown to be advantageous.^{134,135} A higher incidence of esophageal stricture was noted in the group who had both EIS and EVBL.¹³⁶ A more recent meta-analysis confirmed earlier reports that the combination of EIS and EVBL is not superior to EVBL alone in reducing the risk of variceal rebleeding, death or time to variceal obliteration.¹³⁷

Pharmacological versus endoscopic therapy: Studies comparing pharmacological therapy (NSBB plus ISMN) vs. EVBL show no differences in recurrent haemorrhage, but there is a suggestion of a beneficial effect on survival with pharmacological therapy in the long term.^{127,138-141} In one study, the rebleeding rate was higher in the EVBL

group as compared with pharmacological therapy (49% vs. 33% respectively).¹⁴² The risk of recurrent bleeding and of death is significantly lower in patients with haemodynamic response to therapy (defined as a reduction in the HVPG by more than 20% of the baseline value or to less than 12 mmHg). Currently, there is not enough evidence to support the use of the targeted reduction of HVPG in routine clinical practice.¹⁴³

Combined pharmacological and endoscopic therapy: Two prospective trials found the combination of EVBL with medical therapy (Nadolol) superior to EVBL alone.^{144,145} Current recommendation is to use NSBB and EVBL, after initial variceal bleeding, as a means of secondary prophylaxis.²²

TIPSS: In situations of recurrent variceal bleeding despite combined endoscopic and pharmacological therapy, TIPSS with polytetrafluoroethylene (PTFE) covered stents,¹⁴⁶ or where expertise is available, surgical shunts¹⁴⁷ should be provided.

HVPG: Incorporating HVPG in the secondary prophylaxis of variceal bleeding is a relatively new concept. The lowest rates of recurrent variceal haemorrhage (approximately 10%) are observed in individuals who have a hemodynamic response to pharmacologic therapy, defined as a decrease in HVPG to < 12 mmHg or a decrease of > 20% from baseline levels.^{25,148} So in hemodynamic responders to pharmacological therapy, endoscopic treatment would not be necessary. The more rational approach would thus be to guide therapy based on hemodynamic response, however, a small trial showed that outcomes with HVPG-guided therapy are not different from those in patients treated with combined pharmacological and endoscopic therapy.¹⁴⁹ Until the best treatment for non-responders is settled, larger clinical trials are performed, and HVPG measurements are standardized across centers, HVPG-guided therapy cannot be currently recommended.¹⁵⁰

Gastric varices: Rebleeding rates after an acute GV bleeding episode treated with tissue adhesives (mainly cyanoacrylate) range from 7% to 65% with most of the large series reporting rates below 15%.¹⁰³ Similar to what occurs with initial hemostasis, cyanoacrylate (CA) has been shown to be superior to both Sclerotherapy and band ligation for secondary prophylaxis.¹⁰³ On the contrary, comparison with non-selective beta-blockers offers conflicting results. In a small randomized study, comparing repeated cyanoacrylate injections vs. propranolol as secondary prophylaxis, no significant differences were observed between the two groups in the incidence of variceal rebleeding and death. The incidence of complications was higher in the CA group (47% vs. 10%).¹⁵¹ A major limitation of the study was the small number of patients with GV. In a more recent RCT comparing cyanoacrylate vs. propranolol as secondary

prophylaxis, rebleeding in the CA group was significantly lower than in the beta-blocker group (15% vs. 55%, $p=0.004$) and after a 26 months follow-up, the mortality rate was lower as well (3% vs. 25%, $p=0.026$). The rate of complications in the CA group was 3%.¹⁵² In a recent study, patients with GV that bled and were successfully treated with CA were assigned to receive treatment with beta blockers and repeated CA injections or repeated CA injections alone.¹⁵³ The overall rebleeding and survival rates, after a mean follow up of 19 months, were not different between the two groups. One-year rebleeding-free survival was also similar. The result of this study suggests that adding beta blocker therapy to repeated sessions of CA provides no important benefit for prevention of rebleeding and mortality in patients with GV bleeding. Despite these findings, and because non-selective beta-blockers are effective in patients with concomitant esophageal varices, until larger studies with longer follow-up are available, non-selective beta-blockers are still recommended as an adjunct to endoscopic therapy in the prevention of GV rebleeding.¹⁰³

Thrombin is safe and effective in the treatment of acute GV bleeding with hemostasis rates of 70 - 100%, given the paucity of data mostly coming from case series, the routine use of thrombin cannot be routinely recommended for secondary prophylaxis of GV.¹⁰³

TIPSS is a very effective therapy to prevent GV rebleeding, but more data is needed to clarify the role of TIPSS in the secondary prophylaxis of GV bleeding and to determine if this therapy must be universally applied or reserved as a rescue therapy after failure of more conservative approaches.¹⁰²

Surgery has fallen out of favour. In selected cases, patients with gastric varices and segmental/left-sided portal hypertension, due to isolated splenic vein thrombosis, may be candidates for splenectomy or splenic embolization as a means of definitive therapy, however data is scarce.¹⁰³

Although Balloon-occluded Retrograde Trans-venous Obliteration (BRTO) seems to be a feasible technique, able to successfully control and prevent GV bleeding, there is a lack of good quality data to establish the actual place of BRTO on the management of GV. BRTO could be considered in patients with GV bleeding and large gastrosplenic shunts in whom TIPS may be contraindicated (such as those with refractory hepatic encephalopathy or elderly patients).¹⁰³

Recommendations:

1. Candidates: (a) After the control of acute variceal bleeding, secondary prophylaxis must be given to all patients (1a, A); (b) Patients; who require shunt surgery/TIPSS to control the acute episode, do not require further preventive measures. All these patients

should be referred to a transplant center, if they are otherwise a candidate (i.e., CTP score ≥ 7 or a MELD score ≥ 15) (1a, A).

2. Timing: (a) It should be started as soon as possible from day 6 of the index variceal bleeding episode or at the time of discharge (1a,A); (b) The time of start of secondary prophylaxis should be documented (1a, A).

3. Modalities of therapy: (a) Combination of NSBB and endoscopic variceal ligation is the treatment of choice for secondary prophylaxis (1a, A); (b) If endoscopy is not possible, BB alone or in combination with ISMN should be given (1a; A); (c) If BB are contraindicated then EVL is the preferred treatment (5; D).

4. Choice of β -blockers: (a) Propranolol and Nadolol have been extensively studied; however, Carvedilol is an emerging alternative. (b) Carvedilol may be started at a dose of 6.25 mg daily and increased to 6.25 mg twice daily, if clinically tolerated. Carvedilol is as effective as Nadolol plus Isosorbide-5-Mononitrate in the prevention of gastroesophageal variceal rebleeding with fewer severe adverse events and similar survival (1b; A).

5. Endoscopic variceal band ligation: (a) EVBL should be repeated every 2 - 4 weeks until obliteration (1b, A); (b) Following successful eradication of varices, patients should be endoscoped at 3 months and 6 monthly intervals thereafter, to look for recurrence of varices (1b, A); (c) In case of recurrence, band ligation should be repeated (1b, A).

6. Other modalities: (a) TIPSS may be considered in child A or B patients who have recurrent variceal bleed despite combination of pharmacological and endoscopic therapy as secondary prophylaxis (2b; B); (b) Surgical shunts may be considered in Child A/selected Child B patients as an alternative, if TIPSS is unavailable (2b; B); (c) Transplantation provides good long-term outcome in appropriate candidates and should be considered (2b; B); (d) TIPSS may be used as a bridge to transplantation (4, C)

7. Gastric varices: (a) GEV1: Treatment of GEV 1 by EVL or BB is sufficient. GEV1 may be treated with cyanoacrylate injection (2b; B); (b) After the acute episode; patients with GEV 2/IGV1 should receive beta blockers along with repeated sessions of CA injection (1b; A) or TIPSS (2b; B); (c) There is a lack of good quality data to establish the actual place of BRTO in the secondary prophylaxis bleeding from GV.

8. Portal hypertensive gastropathy: (a) BB should be used for prevention of recurrent bleeding in portal hypertensive gastropathy (1b,A).

Areas requiring further studies: The following areas need further studies: incidence and natural history of varices and variceal bleeding (local data needs to be generated), non-invasive techniques to identify patients with clinically significant portal hypertension, the impact

of treating the underlying chronic liver disease in the development of varices and other portal hypertensive related complications, treatments to prevent the development of varices and other portal hypertensive related complications, studies evaluating the use of carvedilol in primary prophylaxis of variceal bleeding, role of NG tube in the setting of acute variceal bleeding, ICU and non-ICU management in resource-constrained country, prophylaxis of PSE in the setting of acute variceal bleeding, optimal duration of vasoactive drug therapy, role of PPIs in the setting of acute variceal bleeding, need for correction of coagulation disorders in the setting of acute variceal bleeding. Influence of coagulopathy and thrombocytopenia on outcome, better stratification of risk to determine timing of the initial endoscopy, duration of drug therapy and type of treatment, best antibiotic in the setting of acute variceal bleeding, role of self-expandable esophageal stents in the setting of acute variceal bleeding, treatment of gastric varices, treatment of pediatric patients, treatment of bleeding ectopic varices like duodenal varices, role of erythromycin before endoscopy, HVPG role in secondary prophylaxis, carvedilol vs. propranolol in secondary prophylaxis, beta-blocker alone or in combination with CA for secondary prophylaxis in GEV2/IGV1; and role of thrombin in secondary prophylaxis in GEV2/IGV1.

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