CLINICAL PRACTICE GUIDELINES

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MANAGEMENT OF ACUTE VARICEAL BLEEDING

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN SOCIETY OF GASTROENTEROLOGY AND HEPATOLOGY

ACADEMY OF MEDICINE OF MALAYSIA

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in May 2007 and will be reviewed in 2010 or sooner if new evidence becomes available.

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GUIDELINE DEVELOPMENT AND OBJECTIVE

GUIDELINE DEVELOPMENT

The clinical practice guidelines on the management of acute variceal bleeding was developed by a team of gastroenterologists, a hepatologist and a surgeon. The information sources and search was carried out using PubMed, Ovid and other search engines using 'variceal bleeding', 'oesophageal varices', 'gastric varices', 'variceal bleeding AND therapy', 'variceal bleeding AND prophylaxis' as keywords and included not only randomised clinical trials or meta-analyses, but also other relevant articles. The recommendations were formulated based on a systematic review of current medical literature, taking into consideration local practice and feedbacks from members of MSGH, general practitioners, physicians and general surgeons during the Annual Scientific Meeting and the MSGH Clinical meeting. Where there is lack of evidence, the recommendation was based on expert opinions, and adapting other international guidelines on Acute Variceal Bleeding and the Proceedings of the Fourth Baveno International Consensus Workshop on Portal Hypertension.

The draft guideline was posted on the Ministry of Health Malaysia website for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

The main objective of this guideline is to present evidence-based recommendations to assist health care professionals in the management of acute variceal bleeding and not meant as a comprehensive overview of all aspects of variceal bleeding.

CLINICAL QUESTIONS

- Could morbidity and mortality associated with acute variceal bleeding be reduced with proper evaluation?
- How can patients with acute variceal bleeding be managed successfully?

TARGET POPULATION

These guidelines are applicable to patients presenting with acute upper gastrointestinal bleeding due to oesophageal or gastric varices.

TARGET GROUP/USER

These guidelines are developed for all health care professionals involved in the evaluation and management of cases with acute variceal bleeding, including general physicians and general surgeons.

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SUMMARY OF RECOMMENDATIONS

RECOMMENDATIONS	GRADE
SCREENING	
Screening endoscopy at the time of diagnosis of cirrhosis and every 2 years in patients not known to have varices	Grade C
OESOPHAGEAL VARICES	
PRIMARY PROPHYLAXIS (of first variceal bleeding)	
Patients with Grade 1 or small varices should not receive primary prophylactic therapy but be screened for enlargement of varices every 1-2 years	Grade C
Patients with large varices (Grade 3) or medium varices (Grade 2) with endoscopic red signs or Child's C cirrhosis should be treated	Grade A
Non-selective beta-blockers or endoscopic variceal ligation reduce the risk of index variceal bleeding. Non-selective beta-blockers is the best available modality for primary prophylaxis at present (survival benefit and cost-effective)	Grade A
MANAGEMENT OF ACUTE OESOPHAGEAL VARICEAL BLEEDING	
Patients should be referred to and treated in units where staff are familiar with the management and the therapeutic interventions to be performed	Grade C
Resuscitation • Haemodynamic monitoring, large bore IV line or central venous access • Blood: group and cross-matched • Correct coagulopathy • Consider intubation for airway protection if severe uncontrollable bleeding, encephalopathic, inability to maintain O_2 saturation adequately and to prevent aspiration • ICU bed and facilities should be made available	Grade C
Institute pharmacotherapy • IV Terlipressin/Octreotide/Somatostatin for 2-5 days to prevent early rebleeding • Terlipressin: 2mg bolus and 1mg every 6 hours for 2-5 days. • Somatostatin: 250mcg bolus followed by 250mcg/hour infusion for 5 days • Octreotide: 50mcg bolus followed by 50mcg/hour for 5 days	Grade A

Antibiotic prophylaxis in patients with cirrhosis • Antibiotic treatment should be continued for 7 days • Norfloxacin 400mg bd **OR** Ciprofloxacin 500mg bd **OR** IV 200mg bd **OR** Third generation cephalosporins (e.g. Ceftriaxone 1g daily)	Grade A
Upper GI Endoscopy • As soon as possible • If endoscopy is unavailable and there is presence of active bleeding, consider balloon tamponade and referral to tertiary centre	 Grade C Grade C
Control of Bleeding • Endoscopic variceal ligation (EVL) is recommended; endoscopic sclerotherapy can be used if EVL is technically difficult	 Grade A
Persistent Active Bleeding • Consider repeating endoscopy, TIPS or surgical intervention • Balloon tamponade may be considered	 Grade B Grade C
SECONDARY PROPHYLAXIS	
Non-selective beta-blockers, EVL or both should be used. However, beta-blockers and EVL are the treatment of first choice	Grade A
TIPS or shunt surgery if non-compliant or refractory to pharmacological and/or endoscopic therapy	Grade B
GASTRIC VARICES	
Gastro-oesophageal varices Type 1 • Treat as for oesophageal varices	 Grade B
Gastro-oesophageal varices Type 2 and isolated gastric varices • For acute bleeding: injection with cyanoacrylate	 Grade A
If persistent active bleeding • TIPS or surgical intervention • Balloon tamponade should be considered	 Grade B Grade C
Secondary prophylaxis • Beta-blockers, injection with cyanoacrylate or TIPS	 Grade B

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1. INTRODUCTION

Gastroesophageal variceal bleeding accounts for 10-30% of upper gastrointestinal haemorrhage and is a major cause of death in patients with cirrhosis.[1] The prevalence of oesophageal varices in patients with cirrhosis varies from 24-81%.[2-5] At the time of diagnosis of cirrhosis, oesophageal varices are present in about 60% of decompensated and 30% of compensated patients.[6]

Variceal bleeding accounts for 6.4% of upper gastrointestinal bleeding in Malaysia.[7] Fifteen percent (105/699) of emergency endoscopy for upper gastrointestinal bleeding performed in Selayang Hospital are due to acute variceal bleeding (unpublished data). The aetiology of cirrhosis in Malaysia is mainly due to hepatitis B or alcohol.[8] The majority of patients who presented with variceal bleeding are Chinese followed by Indians.

2. BACKGROUND

2.1 Oesophageal Varices

Portal hypertension leads to the development of portosystemic collaterals including gastroesophageal varices. The hepatic venous pressure gradient (HVPG), defined as the difference between the wedged/occluded hepatic venous pressure and the free hepatic venous pressure, is the most commonly used parameter to measure portal pressure. The HVPG threshold for the development of varices is 10mmHg (normal HVPG < 5mmHg). However, not all patients with hepatic venous pressure gradient above this level have oesophageal varices.[9] Although the measurement of HVPG is reliable and is a useful adjunct, the procedure is invasive and thus is not widely used in clinical practice.

It is estimated that the annual risk of developing 'de novo' varices after initial diagnosis of cirrhosis is about 5-8% per year.[10,11] The appearance of oesophageal varices has some correlation with the severity of liver disease and portosystemic shunting as well as continued alcohol abuse.[12-14] In alcoholic liver disease, continued abstinence from alcohol may result in a decreasing size or even disappearance of varices. Abstainers have a significantly higher survival rate and a decrease probability of bleeding.

Table 1 : Size classifications of oesophageal varices

Japanese	***US***	***VA Trial***	***Paquet***
Absent	Absent	Absent	Absent
Grade 1: small, straight varices not disappearing with insufflation	Small	< 5 mm	I
Grade 2: medium varices occupying less than one third of the lumen	Medium	5-9 mm	II
Grade 3: large varices occupying more than one third of the lumen	Large	> 9 mm	III
	Giant		IV

To date, there is no consensus on the definition of small varices. Amongst the various classifications of oesophageal varices shown in Table 1,[15-18] the grading developed in Japanese studies is preferred **(Level of evidence III)**. Varices increase in size from small to large at an annual rate of 10-15%.[11] Despite the high occurrence of varices in cirrhotic patients, only 30% of patients with varices will experience variceal haemorrhage.[4,5] The risk of bleeding appears to be greatest within the first year after diagnosis. Mortality of the first bleeding episode is high and ranges between 30% and 50% within 6 weeks;[19] mortality from uncontrolled bleeding in the first instance is between 5-8%.[20] The risk factors for the first episode of variceal bleeding in cirrhotic patients include the severity of the liver dysfunction, the size of the varices (large greater than small), and the presence of endoscopic red wale signs.[4,17,21] Another important risk factor to consider is the hepatic venous pressure gradient (HVPG). It is now well accepted that variceal bleeding will not occur if the HVPG is below 12mmHg.[22] Once this 12mmHg HVPG threshold is crossed, bleeding is expected to occur at some point.

Patients who survived the first bleed from oesophageal varices are at a significant risk of recurrent haemorrhage: 70% of patients will experience recurrent haemorrhage and about a third of further bleeding episodes are fatal.[4,23] Up to fifty percent of recurrent haemorrhage occurs within the first 6 weeks after the index bleed.[20] The risk of re-bleeding is highest during the first

five days, decreases slowly over the first 6 weeks, and becomes virtually equal to that before the index bleed after the sixth week.[19] Risk factors predictive of re-bleeding include the degree of hepatic decompensation, age greater than 60, severity of initial bleed, renal insufficiency, level of portal pressure, size of varices, active bleeding at the time of initial endoscopy and the presence of hepatoma.[20,23]

Recommendation for classification of oesophageal varices
The Japanese classification is the preferred grading scale for the staging of oesophageal varices. **(Grade C)**

2.2 Gastric Varices

Gastric varices 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.[24] Primary gastric varices are varices detected at the time of the first endoscopy, whereas, secondary gastric varices are those which occur within two years of eradication of oesophageal varices. Gastric varices occur five times more often in patients with oesophageal varices that have previously bled than in those that have never bled. Although gastric variceal haemorrhage occurs less frequently than oesophageal variceal haemorrhage, the severity of bleeding and mortality, especially with fundal varices, is greater.[25]

The preferred classification of gastric varices is based on location, size and endoscopic features of the varices:[24,26] gastro-oesophageal varices (GOV) and isolated gastric varices (IGV). GOV extend beyond the gastro-oesophageal junction (OGJ) and are always associated with oesophageal varices. They are further subdivided into Type 1 (GOV I): these varices are a continuation of oesophageal varices and extend for 2-5 cm below the OGJ along the lesser curvature of the stomach. Type 2 (GOV II): these varices extend below the OGJ towards the fundus of the stomach. Gastric varices in the absence of oesophageal varices are termed isolated gastric varices (IGV). Depending on the location, they are subdivided into Type 1 (IGV I): these are located in the fundus of the stomach and fall short of the cardia by a few centimetres. Type 2 (IGV II): these include isolated ectopic varices and can present anywhere in the stomach.

3. PRIMARY PROPHYLAXIS

3.1 Oesophageal Varices

Primary prophylaxis of variceal bleeding is therapy given to patients with known varices to prevent the first episode of variceal haemorrhage. Given the high risk of initial haemorrhage and the high rate of mortality from the first bleeding episode, strategies for prevention of the first bleed are therefore important.

3.1.1 Pharmacological Therapy for Oesophageal Varices

Non-selective ß-adrenergic antagonists such as propranolol and nadolol are widely used in the prevention of the initial bleeding episode. Non-selective rather than selective beta-blockers are more appropriate as blocking $ß_1$ activity causes splanchnic vasoconstriction (by means of reflex á-adrenergic receptors) and by eliminating $ß_2$-receptor mediated splanchnic arterial vasodilation, splanchnic blood flow is reduced.

Beta-blockers have been shown by 3 meta-analyses to statistically reduce the relative risk of bleeding by approximately 45% with a trend towards reducing mortality.[27-29] The average number of patients that are needed to treat to prevent one bleeding episode is 11. The benefit of beta-blockers has been proven in patients with moderate or large varices (>5mm), either with good or poor liver function.[11] Although beta-blocker prophylaxis reduced the rate of variceal bleeding in patients with small oesophageal varices,[30] there is insufficient evidence to support treatment of patients with small varices. Beta-blockers have also been shown to prevent bleeding from portal hypertensive gastropathy.[31]

A cost-effectiveness analysis in the USA supports the use of propranolol as cost-effective in the primary prophylaxis of variceal bleeding.[32] Beta-blocker therapy should be maintained for life as bleeding may occur after stopping treatment.[33] However, the side-effect profile for beta-blocker therapy is considerable: 15-25% of cirrhotic patients are intolerant or have contraindications to beta-blockers that preclude its use.[34]

Other pharmacological alternatives which have been evaluated include nitrates. Although nitrates have been shown to reduce portal pressure, it can potentially worsen the vasodilative haemodynamics typically found in cirrhotic patients. Nitrates were ineffective to prevent variceal bleeding in patients with contraindications or intolerance to beta-blockers and should not be used as

monotherapy to prevent the index variceal bleed.[34] Furthermore, a comparative study between isosorbide mononitrate (ISMN) with propranolol for the prevention of variceal bleeding showed a higher long-term mortality in patients over 50 years of age receiving ISMN.[35] It has been suggested that the higher mortality observed when nitrates was compared to beta-blockers were probably due to a beneficial effect of beta-blockers rather than a real detrimental effect of nitrates.[36]

Recommendations for pharmacological therapy for oesophageal varices

Non-selective beta-blockers is the best available modality for primary prophylaxis at present. **(Grade A)**

3.1.2 Endoscopic Therapy for Oesophageal Varices

Endoscopic treatment modalities available include variceal ligation and injection sclerotherapy. Endoscopic sclerotherapy is based on the concept that bleeding from varices is halted by thrombosis of the bleeding varix by intravariceal or paravariceal injection of a sclerosant. The most commonly used sclerosants are sodium tetradecyl sulphate (thrombovar) and ethanolamine oleate.

There is little, if any, role for endoscopic sclerotherapy in the prevention of the index variceal bleed. A meta-analysis of 20 randomised trials comparing prophylactic endoscopic sclerotherapy with no treatment showed significant heterogeneity between the trials to draw firm conclusions.[37] The risk of side-effects of sclerotherapy probably outweighs the potential benefits and two studies suggest superiority of propranolol over sclerotherapy.[38, 39]

Endoscopic variceal ligation (EVL) is achieved by suction and ligating the varix in a banding device attached to the tip of the endoscope, similar to the technique used for ligation of internal haemorrhoids. Multiband ligators are now available. An initial meta-analysis of 4 randomised clinical trials[40-43] comparing endoscopic ligation and beta-blockers suggested that ligation is superior to beta-blockers in the prevention of variceal bleeding but the risk for mortality was similar in both groups.[44] A further meta-analysis of 5 trials failed to show significant differences between endoscopic ligation and beta-blockers either for bleeding or survival.[36] In a more recent study, although a significantly higher failure rate of variceal bleeding and mortality was noted in patients on beta-blockers compared to those receiving prophylactic EVL, the bleeding rate in the EVL group is unusually low with a relatively short period of follow-up.[45] The

comparison between EVL and beta-blockers versus EVL monotherapy for primary prophylaxis showed no difference between the two groups.[46, 47]

Non-selective beta-blockers is the best available modality for primary prophylaxis at present **(Level of evidence I)**. Prophylactic ligation may be indicated for patients who are intolerant or have contraindications to beta-blockers.

3.2 Gastric Varices

The risk of first bleeding from gastric varices is no greater than that from oesophageal 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.[48]

4. SCREENING ENDOSCOPY

Current guidelines for the primary prophylaxis of oesophageal varices recommend universal screening endoscopy in patients with cirrhosis to identify those who could benefit from therapy. The American College of Gastroenterology and the American Association for the Study of Liver Disease advocate screening endoscopy every other year in patients with cirrhosis not known to have varices. Patients with small varices on initial endoscopy should be screened for enlargement of varices every 1-2 years.[26] A recent analysis by Spiegel et al.[49] suggests that empiric beta-blocker therapy may be a more cost-effective approach in patients with compensated cirrhosis, whereas Arguedas et al.[50] found that this strategy was cost-effective only in patients with decompensated cirrhosis. Until there are more studies comparing screening-directed versus empiric beta-blocker prophylaxis, the recent data should not immediately affect our current practice.

Recommendations for screening endoscopy
Screening endoscopy at the time of diagnosis of cirrhosis and every 2 years in patients not known to have varices. **(Grade C)**

5. MANAGEMENT OF ACUTE VARICEAL BLEEDING

The report of the Baveno IV Consensus Workshop on portal hypertension states the time frame for the acute variceal bleeding episode as 5 days and failure to control bleeding as the need to change specific therapy.[51]

5.1 General Management

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. Therapy is aimed at correcting hypovolumic shock and at achieving haemostasis at the bleeding site. This would be instituted by aggressive resuscitation to restore haemodynamic stability. Two large bore intravenous lines should be in place. Blood volume restitution, preferably packed red blood cells, should be transfused cautiously and conservatively to keep the haemoglobin ideally around 8g/dL or haemocrit of 24%.[52] Overtransfusion should be avoided as this can increase portal pressures and exacerbate further bleeding. If the patient is haemodynamically unstable, elective intubation for airway protection should be considered. Pharmacotherapy to reduce portal pressure should be instituted and emergency endoscopy performed to establish the diagnosis and location of the bleeding site.

5.2 Antibiotics in Acute Variceal Bleeding

Bacterial infections are seen in about 20% of cirrhotics presenting with upper gastrointestinal bleeding within 48 hours.[53,54] The incidence of sepsis increases to almost 66% at two weeks.[50-57] Development of bacterial infection is associated with high mortality and variceal re-bleeding.[54,55] Antibiotic prophylaxis has been shown to reduce the rate of infection, spontaneous bacterial peritonitis and re-bleeding.[56-60] In addition, antibiotic prophylaxis was clearly proven in a meta-analysis to significantly increase the survival rate.[61] 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 **(Level of evidence I)**. As to the choice of antibiotic, either third generation cephalosporins given intravenously or oral quinolones (norfloxacin/ciprofloxacin) are generally recommended.

Recommendations for antibiotics in acute variceal bleeding
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. **(Grade A)**

5.3 Pharmacological Therapy for Acute Variceal Bleeding

Pharmacologic treatment is aimed at arresting haemorrhage by decreasing pressure and blood flow within the oesophageal varices, thus, allowing haemostasis at the bleeding points. Vasoactive drugs have been shown to control acute variceal bleeding in about 80% of patients.[62-68] Vasoactive therapy can be used empirically when variceal bleeding seems likely on clinical grounds. The current recommendation **(Level of evidence I)** is to start a vasoactive drug as early as possible from the time of admission or even upon the patient's transfer to the hospital.[62,63] The agents available are vasopressin (either alone or in combination with nitroglycerine) or its analogues and somatostatin or its analogues. The selection of the vasoactive drug is highly dependent on availability and the treating clinician's familiarity with each.

Vasopressin was the first vasoactive agent used in the treatment of acute variceal bleeding. It does, however, have significant systemic side-effects which include myocardial and mesenteric ischaemia and infarction.[69] The addition of nitroglycerine to vasopressin enhances its efficacy and reduces the cardiovascular side-effects.[70, 71]

Terlipressin, a synthetic vasopressin analogue with fewer side-effects and a longer half-life than vasopressin, is effective in controlling acute variceal bleeding.[72,73] Terlipressin is administered as IV injections of 2mg bolus and 1mg every four to six hours for 2-5 days. A meta-analysis demonstrated that terlipressin was associated with a 34% relative risk reduction in mortality compared to placebo.[72]

Somatostatin and its synthetic analogues, octreotide and vapreotide, control acute variceal bleeding in up to 80% of patients and are generally considered to be equivalent to terlipressin but superior to vasopressin for the control of acute variceal haemorrhage.[73] Somatostatin is given as an IV 250mcg bolus followed by 250mcg/hour infusion. Octreotide is administered as a bolus injection of 50mcg followed by an infusion at a rate of 50mcg/hour. Somatostatin or octreotide therapy should be maintained for 5 days to prevent early re-bleeding.

In acute variceal bleeding, terlipressin may have an added advantage as it can potentially reverse hepatorenal syndrome.[74] In addition, terlipressin has been shown to have a more sustained haemodynamic effect compared to treatment with octreotide.[75]

Recommendations for pharmacological therapy for acute variceal haemorrhage

A vasoactive drug should be started as early as possible from the time of admission or even upon the patient's transfer to the hospital. **(Grade A)**

6. MANAGEMENT OF OESOPHAGEAL VARICEAL BLEEDING

6.1 Endoscopic Therapy

Endoscopic sclerotherapy stops bleeding in 80-90% of patients with acute variceal haemorrhage.[76-78] There was no difference between vasoactive drugs and endoscopic sclerotherapy in failure to control bleeding, early re-bleeding and mortality.[79-81] However, adverse events such as oesophageal ulceration and stricture were significantly more severe with sclerotherapy. Control of bleeding may also be achieved by injection of tissue adhesives e.g. histoacryl/ cyanoacrylate glue. Re-bleeding rates are similar to sclerosants but there is also a higher risk of complications and damage to the endoscopic instrument. This should only be performed by experienced endoscopists when haemostasis has not been achieved.

Endoscopic variceal ligation (EVL) is more effective than sclerotherapy in controlling acute oesophageal variceal bleeding but without a survival advantage.[82-85] EVL is favoured in most settings because it leads to fewer complications and a survival advantage was demonstrated in one study.[85] Technically, banding may be difficult at times because of limited visualisation from bleeding and sclerotherapy is used as it is easier to perform in this setting.

The use of endoscopic therapy alone in the treatment of acute oesophageal variceal bleeding has been challenged as pharmacological therapy is as effective as sclerotherapy, but with significantly less side-effects.[86] However, a meta-analysis on the efficacy of therapeutic regimens in acute variceal bleeding showed that ligation was significantly more successful than pharmacological therapy in the control of ongoing variceal bleeding.[82] Therefore, EVL is recommended for patients with acute variceal bleeding **(Level of evidence I)**.

An important newer approach has been the combination of a vasoactive agent and endoscopic therapy. The addition of vasoactive drugs for a period of five days has been shown to facilitate endoscopy, improve control of bleeding, reduce 5-day re-bleeding rate and transfusion requirements,[87-90] but with no effect on mortality.[91] Combination therapy was beneficial both in low-risk and high-risk patients,[92] even if administered just after the endoscopic procedure.[11,93,94]

Recommendations for endoscopic therapy for acute oesophageal variceal haemorrhage

Endoscopic variceal ligation (EVL) is recommended for patients with acute variceal bleeding. **(Grade A)**

6.2 Balloon Tamponade

Although generally considered effective for stopping bleeding,[95] balloon tamponade is known to have a high re-bleeding rate when the balloon is decompressed and is associated with serious complications such as ulceration, perforation and aspiration pneumonia. In addition, sclerotherapy achieved a higher rate of initial haemostasis compared to balloon tamponade.[96,97] Thus, this should only be considered if facilities for endoscopy are not available prior to transfer to a tertiary centre or as a temporary 'bridge' for a maximum of 24 hours until definitive treatment can be instituted. This should be used in conjunction with pharmacological therapy. The balloon should be kept in the refrigerator, taken out only at the time of the procedure and inserted by a personnel who is familiar with the procedure.

6.3 Transjugular Intrahepatic Portosystemic Shunts (TIPS)

Transjugular intrahepatic portosystemic shunts (TIPS) is effective in the treatment of acute variceal bleeding with a success rate of over 90% in arresting haemorrhage.[98,99] The main limiting factors to the use of TIPS are the high morbidity and mortality:[100,101] the 30-day mortality approaches 100% in patients with advanced liver disease, ongoing sepsis and multi-organ failure.[102] Therefore, the most widely accepted indication for TIPS is as a rescue therapy for uncontrolled variceal bleeding after combined pharmacological and endoscopic therapy **(Level of evidence II)**. Further studies are required to define the role of early TIPS placement in patients with haemodynamically defined (using HVPG measurement) high-risk patients.[103]

Recommendations for Transjugular Intrahepatic Portosystemic Shunts (TIPS)
TIPS is indicated as a rescue therapy for uncontrolled variceal bleeding after combined pharmacological and endoscopic therapy. **(Grade B)**

6.4 Surgical Therapy

Surgical options include oesophageal transection with or without devascularisation, portosystemic shunts and liver transplantation. Regardless of the choice of the surgical technique, morbidity and mortality are high: the 30-day mortality associated with emergency surgical procedures is nearly 80%.[98] Similar to TIPS, the role of surgical therapy in the management of acute variceal bleed has been relegated to salvage haemostatic therapy **(Level of evidence II)**. Liver transplantation is probably only appropriate for liver transplant candidates who bleed while on the waiting list.

Recommendations for surgical therapy
The role of surgical therapy in the management of acute variceal bleed has been relegated to salvage haemostatic therapy. **(Grade B)**

6.5 Secondary Prophylaxis

Secondary prophylaxis is the prevention of recurrent bleeding after a first episode variceal bleed. Secondary prophylaxis should be started from the sixth day of the index variceal bleed.[51]

6.5.1 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 re-bleeding. Beta-blockers are still the mainstay of pharmacotherapy.[104-106] A meta-analysis of 12 randomised controlled trials comparing non-selective beta-blockers to either no treatment or placebo showed a statistically significant reduction in the risk of recurrent bleeding and survival advantage.[107] 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%.[11,108] The number of patients needed to treat in order to prevent one re-bleeding episode is 5, and the number needed to treat in order to prevent a death is 14. Intolerance to propranolol leads to discontinuation of treatment in 30% of patients. Although the addition of isosorbide mononitrate to beta-blockers for secondary prophylaxis appears to be superior to beta-blocker monotherapy in the prevention of variceal re-bleeding, survival benefit was not demonstrated.[108] Therefore, non-selective beta-blockers should be used for secondary prophylaxis **(Level of evidence I)**.

Recommendations for secondary prophylaxis – pharmacological therapy
Non-selective beta-blockers should be used for secondary prophylaxis. **(Grade A)**

6.5.2 Endoscopic Therapy

For the prevention of variceal re-bleeding, endoscopic sclerotherapy is performed every 10-14 days until the varices are obliterated, which typically requires 5 or 6 sessions. Sclerotherapy proved more effective than placebo in terms of prevention of variceal re-bleeding and mortality.[109] However, endoscopic

variceal band ligation has superseded sclerotherapy in the prevention of recurrent oesophageal variceal haemorrhage **(Level of evidence I)** because the risk of re-bleeding is lower than sclerotherapy (approximately 25% vs. 30% respectively at one year), causes fewer complications, requires fewer sessions to eradicate the varices and has a survival benefit.[83,110-113] Similar to sclerotherapy, EVL is performed every 10 to 14 days until the varices are eradicated, which usually takes 3 or 4 sessions. The addition of sclerotherapy to ligation has not been shown to be advantageous:[114,115] a higher incidence of oesophageal stricture was noted in the group who had both sclerotherapy and ligation.[116] A more recent meta-analysis confirmed earlier reports that the combination of EVL and sclerotherapy is not superior to EVL alone in the risk of oesophageal variceal re-bleeding, death or time to variceal obliteration.[117]

Comparison of beta-blockers and isosorbide mononitrate with endoscopic variceal band ligation revealed either no significant difference in the variceal re-bleeding episodes or in survival,[118,119] or significantly less variceal re-bleeding but a higher death rate in the EVL group.[120] In one study, a higher variceal re-bleeding rate was noted in the EVL group as compared with pharmacological therapy (49% vs. 33% respectively).[121] However, pharmacological therapy was found to be effective largely in patients with Child-Pugh A cirrhosis. Noteworthy, the risk of recurrent bleeding and of death was significantly lower in patients who had a haemodynamic response to therapy (defined as a reduction in the HVPG by more than 20% of the baseline value or to less than 12mmHg). Currently, there is not enough evidence to support the use of the targeted reduction of HVPG in routine clinical practice.[122]

Recommendations for secondary prophylaxis – endoscopic therapy
Endoscopic variceal band ligation has superseded sclerotherapy in the prevention of recurrent oesophageal variceal haemorrhage. **(Grade A)**

6.5.3 Combination of Pharmacological and Endoscopic Therapy

The combination of endoscopic therapy and pharmacologic therapy for secondary prophylaxis is attractive and may improve the results of either form of therapy alone. Studies comparing the use of sclerotherapy and beta-blockers showed a lower incidence of variceal re-bleeding than beta-blocker monotherapy but with no improvement in survival.[123,124] The combination of ligation plus ß-adrenergic blockers and sucralfate (EVL to reduce variceal size, nadolol to lower portal pressure and sucralfate to heal oesophageal ulcers) was compared with EVL alone.[125] Triple therapy proved more effective in terms of prevention of variceal re-bleeding; however, no significant difference in death rate was identified. Combination therapy involving endoscopic variceal ligation and beta-adrenergic blockers is probably the preferred treatment but warrants additional trials.[51]

6.5.4 Transjugular Intrahepatic Portosystemic Shunts (TIPS)

TIPS is more effective than endoscopic therapy for the prevention of variceal re-bleeding with 8-18% recurrent variceal bleeding rate at one year:[126-129] shunt dysfunction either due to occlusion or stenosis is almost always the cause. However, TIPS is associated with the occurrence of hepatic encephalopathy in at least 25% of patients after the procedure,[130,131] lacks survival benefit over endoscopic therapy,[132-134] is more costly than pharmacological therapy[135] and therefore, should not be used as a first-choice treatment for secondary prophylaxis.

6.5.5 Surgical Therapy

Prevention of recurrent variceal bleeding with surgery may be more effective than pharmacological or endoscopic therapy in patients with preserved synthetic function provided that it is performed by an experienced surgeon.[136-139] Portal blood flow-preserving procedures such as selective shunts or devascularisation procedures appears to be better than decompressive surgical shunts with re-bleeding rate of 6% vs. 14.3% and postoperative encephalopathy of 6% vs. 21% respectively.[140,141] In addition, selective shunts do not exclude the patients for future liver transplantation.

In comparison with TIPS, surgical shunts are significantly more invasive but placement of TIPS resulted in higher re-bleeding rate[142] and cost[143] than surgical shunt due to subsequent occlusion and re-bleeding with no significant effect on mortality. TIPS is most suited for patients with Child's B or C cirrhosis, particularly those who are candidates for liver transplantation while surgical shunts should be limited to patients with Child's A cirrhosis.[144]

Secondary prophylaxis with TIPS or surgical shunt is preferred for patients who are non-compliant with pharmacological or endoscopic therapy **(Level of evidence II)**.

Recommendations for secondary prophylaxis – surgical therapy
Secondary prophylaxis with TIPS or surgical shunt is preferred for patients who are non-compliant with pharmacological or endoscopic therapy.
(Grade B)

7. MANAGEMENT OF ACUTE GASTRIC VARICEAL BLEEDING

The treatment goals for acute gastric variceal bleeding are the same as for oesophageal varices: to control acute bleeding and prevent re-bleeding. Indications for treatment are: active bleeding from varices, stigmata of recent bleeding episode on gastric varices, history of a previous bleeding episode and presence of gastric varices as the only source of bleeding.

7.1 Gastro-Oesophageal Varices (GOV) Type 1

Treat as for oesophageal varices **(Level of evidence II)**.

Recommendations for GOV type 1
Treat as for oesophageal varices. **(Grade B)**

7.2 Gastro-Oesophageal Varices (GOV) Type 2 and Isolated Gastric Varices (IGV)

7.2.1 Endoscopic Therapy

Injection of cyanoacrylate glue has been shown to achieve haemostasis in 90% of acutely bleeding gastric varices[145-147] and has been shown to be better than alcohol and band ligation.[148,149] It is important to ensure the intravariceal position of the needle. Histoacryl is mixed with lipiodol in a ratio of 0.5:0.8ml. Histoacryl should be injected in a slow and controlled fashion and should not exceed 2ml as there is a risk of thrombotic complications including pulmonary embolism. These procedures should only be performed by experienced endoscopists.

For acute GOV Type 2 and IGV: injection with cyanoacrylate **(Level of evidence I)**.

Recommendations for GOV type 2 and IGV
For acute bleeding: injection with cyanoacrylate. **(Grade A)**

7.2.2 Balloon Tamponade

Immediate control of bleeding from all types of gastric varices except IGV II can be obtained by using the Sengstaken-Blakemore tube with the gastric balloon held under traction.

7.2.3 Transjugular Intrahepatic Portosystemic Shunts (TIPS)

This is the treatment modality when bleeding GOV is not responsive to endoscopic and pharmacological treatment.

7.2.4 Secondary Prophylaxis

Data on long-term outcome after GOV obliteration are scanty. In general, recurrence after obliteration is much lower in patients with gastric varices than in patients with oesophageal varices except for patients with fundal varices.[150] Cyanoacrylate glue was shown to be more effective than alcohol sclerotherapy for the control of variceal re-bleeding (100% vs. 44% respectively).[149] TIPS and surgical intervention are the other therapeutic options for gastric variceal re-bleeding. TIPS has been shown to be effective in patients with gastric varices in terms of re-bleeding and survival.[151,152]

8. CONCLUSION

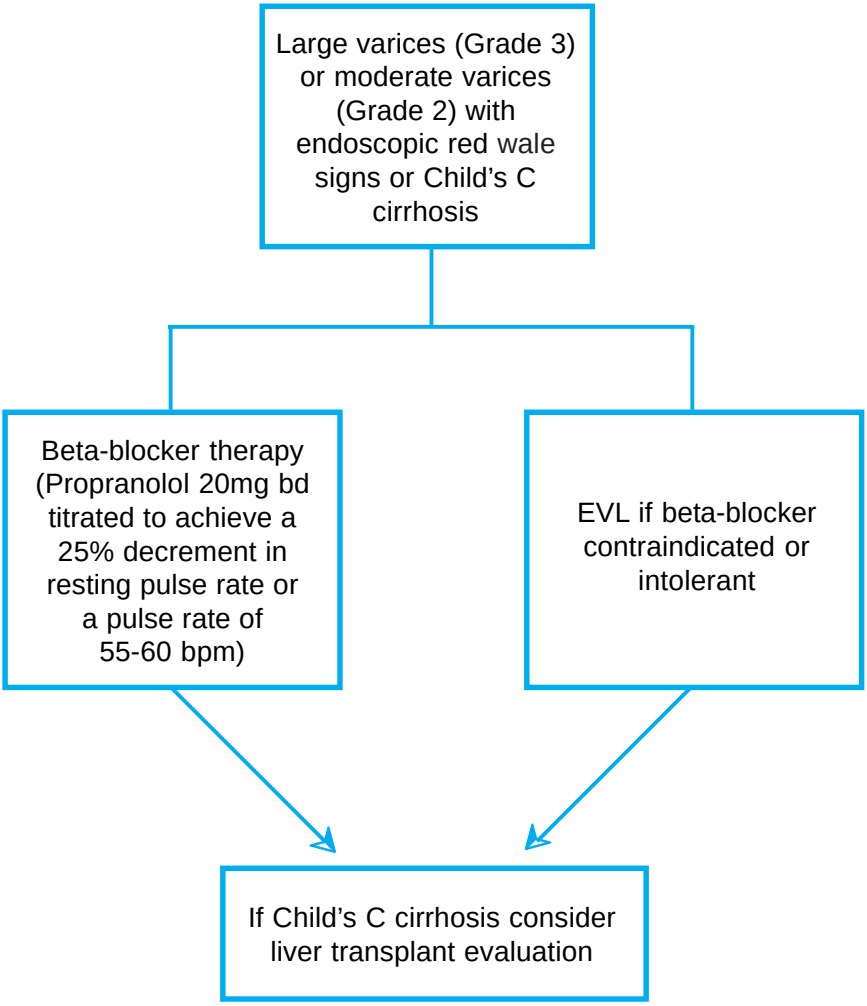
The current first choice treatment in patients with oesophageal varices who have not bled is prophylactic non-selective beta-blocker therapy. Therapy with beta-blockers is cheap, easy to administer, and significantly reduces the risk of index variceal haemorrhage. Only patients with Grade 3 (large varices), Grade 2 (moderate varices) with endoscopic red wale signs or Child's C cirrhosis should be offered this therapy. Typically, the initial dose of propranolol is 20mg twice daily with the dose titrated to achieve a 25% decrement in resting pulse rate or a pulse rate of 55-60 bpm. Endoscopic variceal band ligation may be an alternative for patients who cannot tolerate, or have contraindications to beta-blockers.

The best approach for patients with acute variceal bleeding is the combination of vasoactive drugs and endoscopic therapy. Terlipressin is administered as 2mg IV bolus and 1mg every six hours for 2-5 days. Somatostatin is given as an IV 250mcg bolus followed by 250mcg/hour infusion and octreotide is administered as a bolus injection of 50mcg followed by an infusion at a rate of 50mcg/hour. Somatostatin or octreotide therapy should be maintained for 5 days to prevent early re-bleeding.

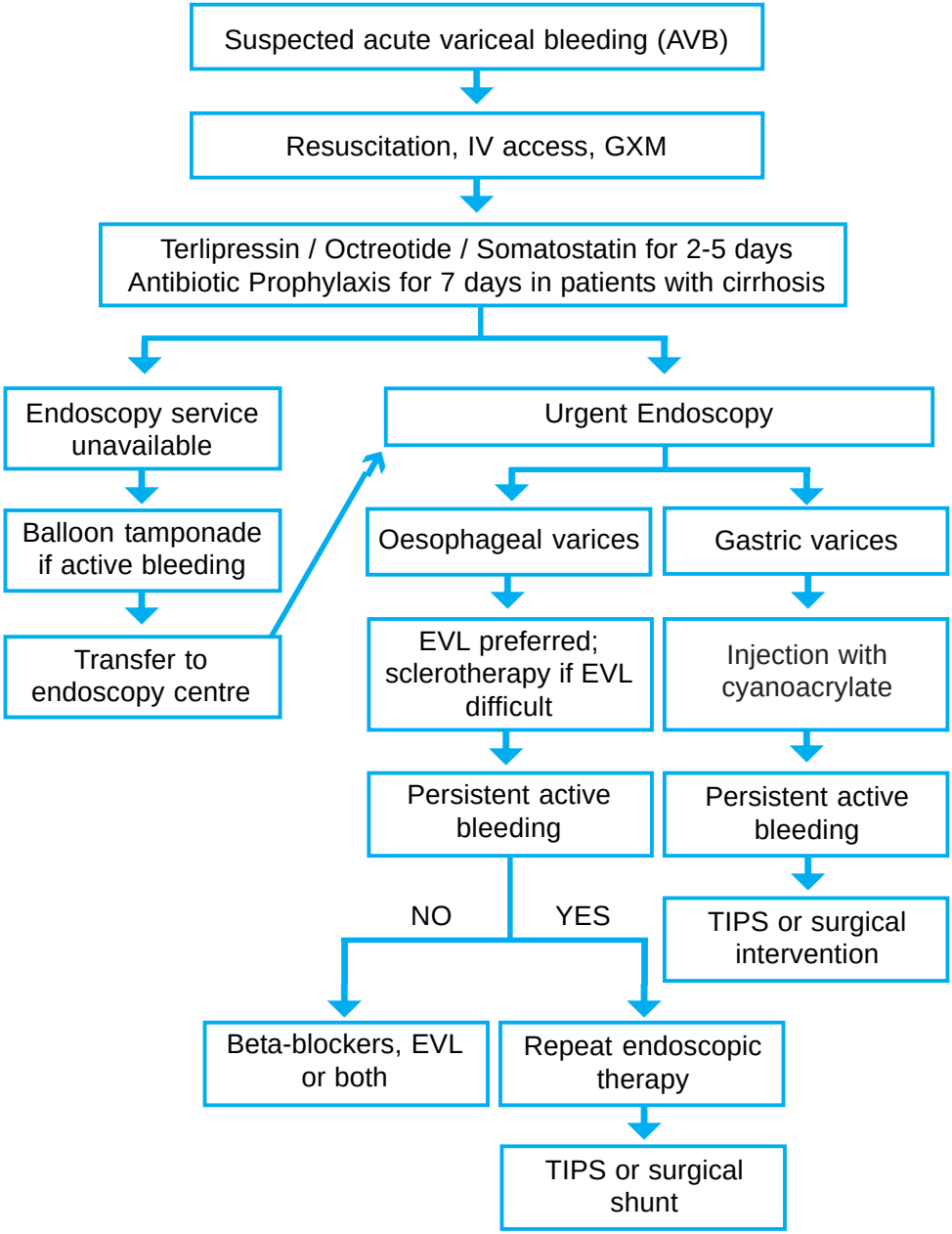
Regarding endoscopic therapy, EVL is preferred but sclerotherapy may be used depending on the endoscopist's experience and the particular circumstances found during endoscopy.

The first-line treatment for prevention of recurrent variceal haemorrhage is beta-blockers, endoscopic variceal ligation or the combination of beta-blockers and endoscopic variceal ligation. TIPS or surgical shunt appears to be more appropriate for patients who are non-compliant or refractory to pharmacological and endoscopic therapy.

ALGORITHM: PRIMARY PROPHYLAXIS OF VARICEAL BLEED



ALGORITHM: MANAGEMENT OF ACUTE VARICEAL BLEEDING



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LEVELS OF EVIDENCE SCALE & GRADES OF RECOMMENDATIONS

Similar to the clinical practice guidelines on acute non-variceal upper gastrointestinal bleeding, the grading of the quality of evidence and the strength of each recommendation are as follows

LEVELS OF EVIDENCE SCALE

Level	
I	Evidence obtained from at least one properly randomised controlled trial
II - 1	Evidence obtained from well-designed controlled trials without randomization
II - 2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II - 3	Evidence obtained from multiple time series with or without the intervention.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

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GRADES OF RECOMMENDATIONS

Grade A	Evidence from large, randomised clinical trials or meta-analyses
Grade B	High quality study of non-randomised cohorts who did not receive therapy or high quality case series
Grade C	Opinions from experts based on arguments from physiology bench research or first principles