

CLINICAL PRACTICE GUIDELINES

May 2007

MOH/P/PAK/125.07 (GU)

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 <ul style="list-style-type: none"> • 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 O₂ saturation adequately and to prevent aspiration • ICU bed and facilities should be made available 	Grade C
Institute pharmacotherapy <ul style="list-style-type: none"> • 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

<p>Antibiotic prophylaxis in patients with cirrhosis</p> <ul style="list-style-type: none"> • 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) <p>Upper GI Endoscopy</p> <ul style="list-style-type: none"> • As soon as possible • If endoscopy is unavailable and there is presence of active bleeding, consider balloon tamponade and referral to tertiary centre <p>Control of Bleeding</p> <ul style="list-style-type: none"> • Endoscopic variceal ligation (EVL) is recommended; endoscopic sclerotherapy can be used if EVL is technically difficult <p>Persistent Active Bleeding</p> <ul style="list-style-type: none"> • Consider repeating endoscopy, TIPS or surgical intervention • Balloon tamponade may be considered <p>SECONDARY PROPHYLAXIS</p> <p>Non-selective beta-blockers, EVL or both should be used. However, beta-blockers and EVL are the treatment of first choice</p> <p>TIPS or shunt surgery if non-compliant or refractory to pharmacological and/or endoscopic therapy</p>	<p>Grade A</p> <p>Grade C Grade C</p> <p>Grade A</p> <p>Grade B Grade C</p> <p>Grade A</p> <p>Grade B</p>
GASTRIC VARICES	
<p>Gastro-oesophageal varices Type 1</p> <ul style="list-style-type: none"> • Treat as for oesophageal varices <p>Gastro-oesophageal varices Type 2 and isolated gastric varices</p> <ul style="list-style-type: none"> • For acute bleeding: injection with cyanoacrylate <p>If persistent active bleeding</p> <ul style="list-style-type: none"> • TIPS or surgical intervention • Balloon tamponade should be considered <p>Secondary prophylaxis</p> <ul style="list-style-type: none"> • Beta-blockers, injection with cyanoacrylate or TIPS 	<p>Grade B</p> <p>Grade A</p> <p>Grade B Grade C</p> <p>Grade B</p>

TABLE OF CONTENTS

GUIDELINE DEVELOPMENT AND OBJECTIVE	i
GUIDELINE DEVELOPMENT COMMITTEE	iii
SUMMARY OF RECOMMENDATIONS	v
1. INTRODUCTION	1
2. BACKGROUND	1
2.1 Oesophageal Varices	1
2.2 Gastric Varices	3
3. PRIMARY PROPHYLAXIS	4
3.1 Oesophageal Varices	4
3.1.1 Pharmacological Therapy for Oesophageal Varices	4
3.1.2 Endoscopic Therapy for Oesophageal Varices	5
3.2 Gastric Varices	6
4. SCREENING ENDOSCOPY	6
5. MANAGEMENT OF ACUTE VARICEAL BLEEDING	7
5.1 General Management	7
5.2 Antibiotics in Acute Variceal Bleeding	7
5.3 Pharmacological Therapy for Acute Variceal Bleeding	8
6. MANAGEMENT OF OESOPHAGEAL VARICEAL BLEEDING	9
6.1 Endoscopic Therapy	9
6.2 Balloon Tamponade	10
6.3 Transjugular Intrahepatic Portosystemic Shunts (TIPS)	10
6.4 Surgical Therapy	10
6.5 Secondary Prophylaxis	11
6.5.1 Pharmacological Therapy	11
6.5.2 Endoscopic Therapy	11
6.5.3 Combination of Pharmacological and Endoscopic Therapy	12
6.5.4 Transjugular Intrahepatic Portosystemic Shunts (TIPS)	13
6.5.5 Surgical Therapy	13
7. MANAGEMENT OF ACUTE GASTRIC VARICEAL BLEEDING	14
7.1 Gastro-Oesophageal Varices (GOV) Type 1	14
7.2 Gastro-Oesophageal Varices (GOV) Type 2 and Isolated Gastric Varices (IGV)	14
7.2.1 Endoscopic Therapy	14
7.2.2 Balloon Tamponade	14
7.2.3 Transjugular Intrahepatic Portosystemic Shunts (TIPS)	14
7.2.4 Secondary Prophylaxis	15
8. CONCLUSION	15
ALGORITHMS	16
REFERENCE	18
ACKNOWLEDGEMENT	25
DISCLOSURE STATEMENT	25
SOURCES OF FUNDING	25

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

<i>Japanese</i>	<i>US</i>	<i>VA Trial</i>	<i>Paquet</i>
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 β -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 β_1 activity causes splanchnic vasoconstriction (by means of reflex α -adrenergic receptors) and by eliminating β_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 trials⁴⁰⁻⁴³ 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 β -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 therapy¹³⁵ 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 rate¹⁴² and cost¹⁴³ 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 varices¹⁴⁵⁻¹⁴⁷ 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

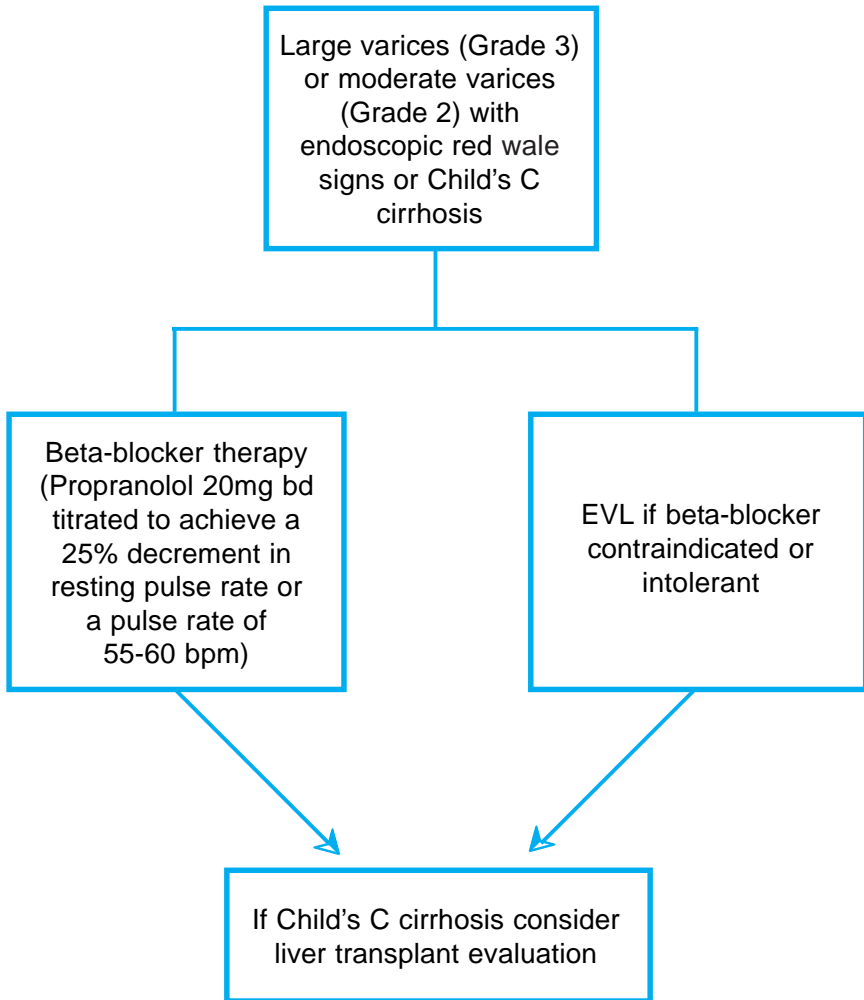
The current first choice treatment in patients with oesophageal varices who have not bled is prophylactic non-selective beta-blocker therapy. Therapy with beta-blockers is cheap, easy to administer, and significantly reduces the risk of index variceal haemorrhage. Only patients with Grade 3 (large varices), 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.

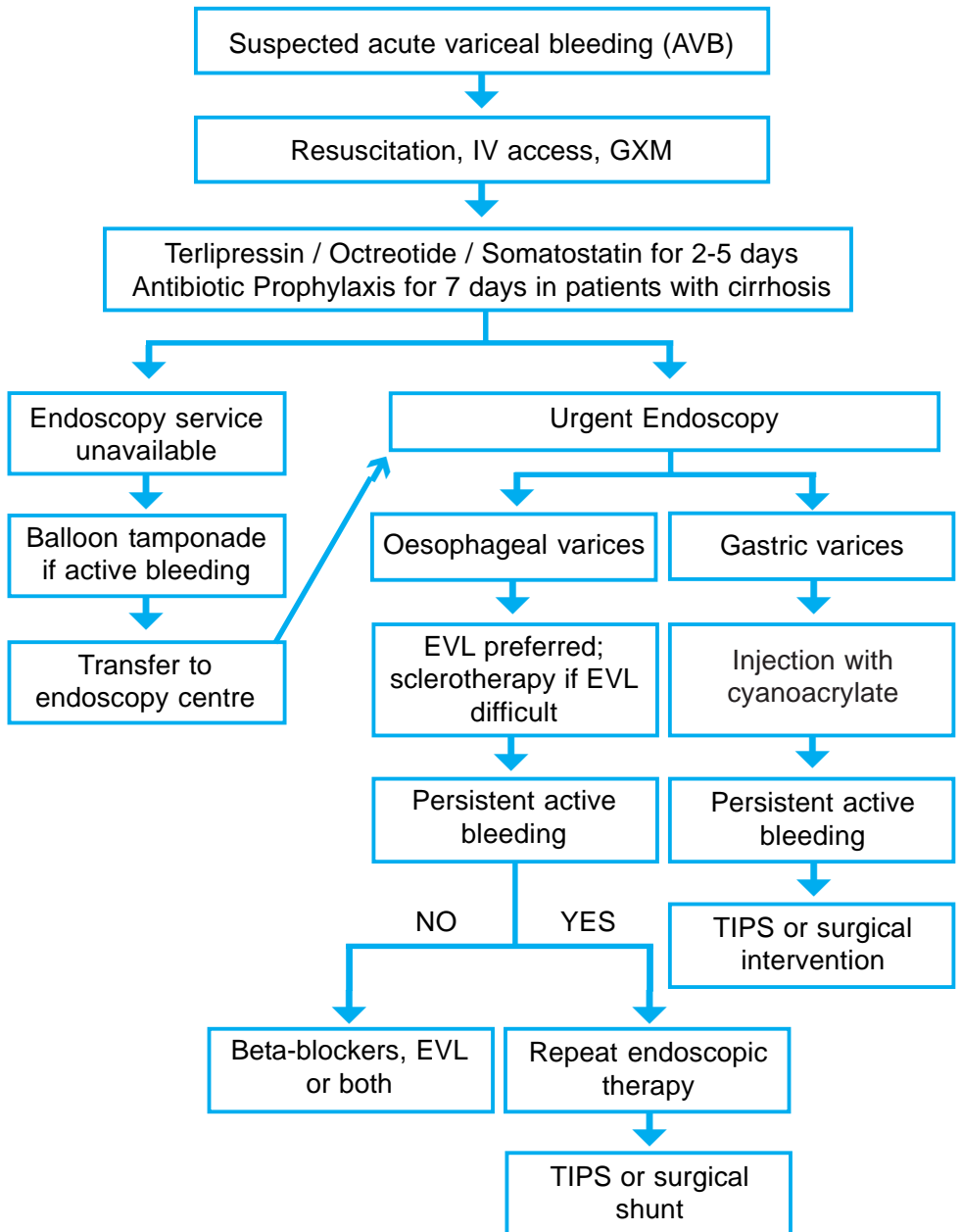
Regarding endoscopic therapy, EVL is preferred but sclerotherapy may be used depending on the endoscopist's experience and the particular circumstances found during endoscopy.

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



REFERENCES

1. Laine L. Upper gastrointestinal tract hemorrhage. *West J Med.* 1991;155:274-9.
2. Schepis F, Camma C, Niceforo D, et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection. *Hepatology.* 2001;33:333-8.
3. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. *Baillieres Best Pract Res Clin Gastroenterol.* 1997;11:243-56.
4. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N Engl J Med.* 1988;319:983-9.
5. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomised trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology.* 1990;99:1401-7.
6. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension. A meta-analytic review. *Hepatology.* 1995;22:332-54.
7. Cheng JLS, Gunn A, Menon J, et al. Aetiology of acute upper gastrointestinal bleeding in East Malaysia. *Med J Mal.* 2001;56(supp A) D31.
8. Rosmawati M, Tan YM, Ranjeev P, et al. The aetiology of variceal bleeding in Malaysia. *J Gastroenterol Hepatol.* 1999;14(Suppl):S108-9.
9. Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology.* 1985;5:419-24
10. Christensen E, Faverholdt L, Schlichting P, et al. Aspects of natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisolone. *Gastroenterology.* 1981;81:944-52.
11. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis.* 1999;19:475-505.
12. Cales P, Pascal JP. Natural history of oesophageal varices in cirrhosis (from origin to rupture). *Gastroenterol Clin Biol.* 1990;12:245-54.
13. Baker LA, Smith C, Lieberman G. The natural history of esophageal varices. *Am J Med.* 1959;26:228-37.
14. Dagradi A. The natural history of esophageal varices in alcoholic liver disease. *Am J Gastroenterol.* 1972;57:520-40.
15. El-Serag HB, Everhart JE. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. *Am J Gastroenterol.* 2000;95:3566-73.
16. Paquet KJ. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices – a prospective controlled randomised trial. *Endoscopy.* 1982;14:4-5.
17. Beppu K, Inokuchi K, Koyanagi N, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc.* 1981;27:213-8.
18. Endo M, Fujita R. Panel discussion. Esophageal varices and endoscopy. *Gastrointest Endosc.* 1983;25:1827-61.
19. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology.* 1981;80:800-9.
20. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis.* 2001;5:645-63.
21. de Franchis R. Prediction of the 1st variceal hemorrhage in patients with cirrhosis of the liver and esophageal-varices; a prospective multicentre study. *N Engl J Med.* 1988;319:983-9.
22. Armonis A, Patch D, Burroughs AK. Hepatic venous pressure measurement: An old test as new prognostic marker in cirrhosis? *Hepatology.* 1997;2:245-8.
23. de Franchis R, Primignani M. Why do varices bleed? *Gastroenterol Clin North Am.* 1992;2:85-101.

24. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology*. 1992;16:1343-9.
25. Kim T, Shijo H, Kokawa H, et al. Risk factors for hemorrhage from gastric fundal varices. *Hepatology*. 1997;25:307-12.
26. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol*. 2000;33:846-52.
27. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology*. 1995;22:332-54.
28. Hayes PC, Davis JM, Lewis JA, et al. Meta-analysis of the value of propranolol in the prevention of variceal haemorrhage. *Lancet*. 1990;336:153-6.
29. Poynard T, Cales P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. Franco-Italian Multicenter Study Group. *N Engl J Med*. 1991;324:1532-8.
30. Merkel C, Marin R, Angeli P, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology*. 2004;127(2):476-84.
31. Perezayuso RM, Pique JM, Bosch J, et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. *Lancet*. 1991;337:1431-4.
32. Teran JC, Imperiale TF, Mullen KD, et al. Primary prophylaxis of variceal bleeding in cirrhosis: a cost-effectiveness analysis. *Gastroenterology*. 1997;112:473-82.
33. Abraczinskas DR, Ookubo R, Grace ND, et al. Propranolol for the prevention of first esophageal variceal hemorrhage: a lifetime commitment? *Hepatology*. 2001 Dec;34(6):1096-102.
34. Garcia-Pagan JC, Villanueva C, Vila MC, et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. *Gastroenterology*. 2001 Oct;121(4):908-14.
35. Angelico M, Carli Z, Piat C, et al. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. *Gastroenterology*. 2000;113:1632-9.
36. Garcia-Pagan JC. Non-selective beta-blockers in the prevention of first variceal bleeding. Is there a definite alternative? *J Hepatol*. 2002;37:393-5.
37. Pagliaro L, D'Amico G, Sorensen TIA, et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomised clinical trials of nonsurgical treatment. *Ann Intern Med*. 1992;117:59-70.
38. de Franchis R, Primignani M, Arcidiacono PG, et al. Prophylactic sclerotherapy in high-risk cirrhotics selected by endoscopic criteria. A multicenter randomised controlled trial. *Gastroenterology*. 1989;101:1087-93.
39. The PROVA Study Group. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: a randomised multicenter trial. *Hepatology*. 1991;14:1016-24.
40. Sarin SK, Guptan RC, Jain AK, et al. A randomised controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. *Eur J Gastroenterol Hepatol*. 1996;8:337-42.
41. Lui HF, Stanley AJ, Forrest EH, et al. Primary prophylaxis of variceal hemorrhage: a randomised controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology*. 2002;123(3):735-44.
42. Chen CY, Sheu MZ, Su SY. Prophylactic endoscopic variceal ligation for esophageal varices. *Gastroenterology*. 1998;114:1224A.
43. De BK, Ghoshal UC, Das T, et al. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomised controlled trial. *J Gastroenterol Hepatol*. 1999;14:220-4.
44. Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. *Hepatology*. 2001;33:802-7.
45. Jutabha R, Jensen DM, Martin P, et al. Randomised study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. *Gastroenterology*. 2005;128(4):870-81.

46. Sarin SK, Wadhawan M, Agrawal SR, et al. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol.* 2005 Apr;100(4):797-804.
47. Chalasani N, Boyer TD. Primary prophylaxis against variceal bleeding: beta-blockers, endoscopic ligation, or both? *Am J Gastroenterol.* 2005 Apr;100(4):805-7.
48. Binmoeller KF. Glue for gastric varices: some sticky issues. *Gastrointest Endosc.* 2000;52:298-301.
49. Spiegel BM, Targownik L, Dulai GS, et al. Endoscopic screening for esophageal varices in cirrhosis: Is it ever cost effective? *Hepatology.* 2003;37(2):366-77.
50. Arguedas MR, Heudebert GR, Eloubeidi MA, et al. Cost-effectiveness of screening, surveillance, and primary prophylaxis strategies for esophageal varices. *Am J Gastroenterol.* 2002 Sep;97(9):2441-52.
51. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol.* 2005 Jul;43(1):167-76.
52. Hochain P, Merle V, Tuil S, et al. Transfusion for variceal bleeding in cirrhotic patients. *Gut.* 1996;38(1):154.
53. Bleichner G, Boulanger R, Squara P, et al. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. *Br J Surg.* 1986;73:724-6.
54. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology.* 1995;108:1828-34.
55. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998;27:1207-12.
56. Rimola A, Bory F, Teres J, et al. Oral, non-absorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. *Hepatology.* 1985;5:463-7.
57. Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. *Gastroenterology.* 1992;103:1267-72.
58. Blaise M, Pateron D, Trinchet JC, et al. Systemic antibiotic therapy prevents bacterial infections in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology.* 1994;20:34-8.
59. Pauwels A, Mostefa-Kara N, Debenes B, et al. Antimicrobial prophylaxis after gastrointestinal hemorrhage for cirrhotic patients with a high risk of infection. *Hepatology* 1996;24:802-6.
60. Hsieh WJ, Lin HC, Hwang SJ, et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. *Am J Gastroenterol.* 1998;93:962-6.
61. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology.* 1999;29(6):1655-61.
62. Burroughs AK, Patch DW. Management of variceal haemorrhage in cirrhotic patients. *Gut.* 2001;48:738-40.
63. Levacher S, Letoumelin P, Pateron D, et al. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet.* 1995;346:865-8.
64. Kravetz D, Bosch J, Teres J, et al. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. *Hepatology.* 1984 May-Jun;4(3):442-6.
65. Jenkins SA, Baxter JN, Corbett W, et al. A prospective randomised controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal haemorrhage. *Br Med J (Clin Res Ed).* 1985;290(6464):275-8.
66. Bagarani M, Albertini V, Anza M. Effect of somatostatin in controlling bleeding from esophageal varices. *Ital J Surg Sci.* 1987;17(1):21-6.
67. Saari A, Klvilaakso E, Inberg M, et al. Comparison of somatostatin and vasopressin in bleeding esophageal varices. *Am J Gastroenterol.* 1990;85(7):804-7.
68. Hwang SJ, Lin HC, Chang CF, et al. A randomised controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol.* 1992;16(3):320-5.
69. Conn HO, Ramsby GR, Storer EH, et al. Intraarterial vasopressin in the treatment of upper gastrointestinal hemorrhage: a prospective, controlled clinical trial. *Gastroenterology.* 1975;68:211-21.

70. Bosch J, Groszmann RJ, Garcia-Pagan JC, et al. Association of transdermal nitroglycerin to vasopressin infusion in the treatment of variceal hemorrhage: a placebo-controlled clinical trial. *Hepatology*. 1989;10:962-8.
71. Gimson AE, Westaby D, Hegarty J, et al. A randomised trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. *Hepatology*. 1986;6:410-3.
72. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev*. 2003;(1):CD002147
73. Feu F, Ruiz del Arbol L, Banares R, et al. Double-blind randomised controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. *Gastroenterology*. 1996;111:1291-9.
74. Ortega R, Gines P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomised study. *Hepatology*. 2002;36 (4 pt 1):941-8.
75. Baik SK, Jeong PH, Ji SW, et al. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomised comparison. *Am J Gastroenterol*. 2005;100(3):631-5.
76. Westaby D, Hayes PC, Gimson AE, et al. Controlled clinical trial of injection sclerotherapy for active variceal bleeding. *Hepatology*. 1989;9:274-7.
77. Burroughs AK, Hamilton G, Phillips A, et al. A comparison of sclerotherapy with staple transection of the esophagus for the emergency control of bleeding from esophageal varices. *N Engl J Med*. 1989;321:857-62.
78. Lo GH, Lai KH, Ng WW, et al. Injection sclerotherapy preceded by esophageal tamponade versus immediate sclerotherapy in arresting active variceal bleeding: a prospective randomised trial. *Gastrointest Endosc*. 1992;38:421-4.
79. Sung JJ, Chung SC, Lai CW, et al. Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. *Lancet*. 1993;342:637-41.
80. Escorsell A, Ruiz del Arbol L, Planas R, et al. Multicenter randomised controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology*. 2000;32:471-6.
81. Jenkins SA, Shields R, Davies M, et al. A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut*. 1997;41:526-33.
82. Gross M, Schieman U, Muhlhofer A, et al. Meta-analysis: efficacy of therapeutic regimens in ongoing variceal bleeding. *Endoscopy*. 2001 Sep;33(9):737-46.
83. Laine L, el-Newihi HM, Migikovsky B, et al. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med*. 1993;119:1-7.
84. Lo GH, Lai KH, Cheng JS, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology*. 1997;25:1101-4.
85. Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med*. 1992;326:1527-32.
86. D'Amico G, Pietrosi G, Tarantino I, et al. Emergency sclerotherapy versus medical interventions for bleeding oesophageal varices in cirrhotic patients (Cochrane review). *Cochrane Database Syst Rev*. 2002;CD002233.
87. Avgerinos A, Nevens F, Raptis S, et al. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European acute bleeding oesophageal variceal episodes (ABOVE) randomised trial. *Lancet*. 1997;350:1495-9.
88. Cales P, Masliah C, Bernard B, et al. Early administration of vapreotide for variceal bleeding in patients with cirrhosis. French club for the study of portal hypertension. *N Engl J Med*. 2001;344:23-8.
89. Besson I, Ingrand P, Person B, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med*. 1995;333:555-60.
90. Sung JJ, Chung SC, Yung MY, et al. Prospective randomised study of effect of octreotide on re-bleeding from oesophageal varices after endoscopic ligation. *Lancet*. 1995;346:1666-9.

91. Banares R , Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology*. 2002;35:609-15.
92. Villanueva C, Ortiz J, Sabat M, et al. Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal variceal bleeding: a prospective randomised trial. *Hepatology*. 1999;30:384-9.
93. Corley DA, Cello JP, Adkisson W, et al. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology*. 2001;120:946-54.
94. Abraldes JG, Bosch J. Somatostatin and analogues in portal hypertension. *Hepatology*. 2002;35:1305-12.
95. Fort E, Sautereau D, Silvain C, et al. A randomised trial of terlipressin plus nitroglycerin vs. balloon tamponade in the control of acute variceal hemorrhage. *Hepatology*. 1990;11:678-81.
96. Paquet KJ, Feussner H. Endoscopic sclerosis and esophageal balloon tamponade in acute hemorrhage from esophagogastric varices: a prospective controlled randomised trial. *Hepatology*. 1985 Jul-Aug;5(4):580-3.
97. Moreto M, Zaballa M, Bernal A, et al. A randomised trial of tamponade or sclerotherapy as immediate treatment for bleeding esophageal varices. *Surg Gynecol Obstet*. 1988 Oct;167(4):331-4.
98. Jalan R, John TG, Redhead DN, et al. A comparative study of emergency transjugular intrahepatic portosystemic stent-shunt and esophageal transection in the management of uncontrolled variceal hemorrhage. *Am J Gastroenterol*. 1995;90:1932-7.
99. Sanyal AJ, Freedman AM, Luketic VA, et al. Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology*. 1996;111:138-46.
100. J. Bosch. Salvage transjugular intrahepatic portosystemic shunt: is it really life-saving? *J Hepatol*. 2001;35:658-60.
101. Azoulay D, Castaing D, Majno P, et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. *J Hepatol*. 2001;35:590-7.
102. Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt. *Semin Liver Dis*. 1999;19:457-73.
103. Monescillo A, Martinez-Lagares F, Ruiz del Arbol L, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology*. 2004;40(4):793-801.
104. Burroughs AK, Jenkins WJ, Sherlock S, et al. Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. *N Engl J Med*. 1983;309:1539-42.
105. Lebrec D, Poynard T, Bernuau J, et al. A randomised controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a final report. *Hepatology*. 1984;4:355-8.
106. Villeneuve JP, Pomier-Layrargues G, Infante-Rivard C, et al. Propranolol for the prevention of recurrent variceal hemorrhage: a controlled trial. *Hepatology*. 1986;6:1239-43.
107. Bernard B, Lebrec D, Mathurin P, et al. Beta-adrenergic antagonists in the prevention of gastrointestinal re-bleeding in patients with cirrhosis: a meta-analysis. *Hepatology*. 1997;25:63-70.
108. Gournay J, Masliah C, Martin T, et al. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal re-bleeding. *Hepatology*. 2000;31:1239-45.
109. Goulis J, Burroughs AK. Portal Hypertensive bleeding: prevention and treatment. In: McDonald J, Burroughs A, Feagan B, (eds). *Evidence Based Gastroenterology and Hepatology*. London: BMJ Books, 1999:389-426.
110. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. *Ann Intern Med*. 1995;123:280-7.
111. Heresbach D, Jacquelinet C, Nouel O, et al. Sclerotherapy versus ligation in hemorrhage caused by rupture of esophageal varices. Direct meta-analysis of randomised trials. *Gastroenterol Clin Biol*. 1995 Nov;19(11):914-20.
112. Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med*. 1992;326:1527-32.

113. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomised trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology*. 1995;22:466-71.
114. Saeed ZA, Stiegmann GV, Ramirez FC, et al. Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: a multicenter prospective randomised trial. *Hepatology*. 1997;25:71-4.
115. Laine L, Stein C, Sharma V. Randomised comparison of ligation versus ligation plus sclerotherapy in patients with bleeding esophageal varices. *Gastroenterology*. 1996;110:529-33.
116. Singh P, Pooran N, Indaram A, et al. Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: a meta-analysis. *Am J Gastroenterol*. 2002;97:623-9.
117. Karsan HA, Morton SC, Shekelle PG, et al. Combination endoscopic band ligation and sclerotherapy compared with endoscopic band ligation alone for the secondary prophylaxis of esophageal variceal hemorrhage: a meta-analysis. *Dig Dis Sci*. 2005;50(2):399-406.
118. Patch D, Sabin CA, Goulis J, et al. A randomised, controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal re-bleeding in patients with cirrhosis. *Gastroenterology*. 2002;123:1013-9.
119. Agrawal SR, Gupta R, Murthy NS, et al. Comparable efficacy of propranolol plus isosorbide mononitrate and endoscopic variceal ligation in prevention of variceal rebleed. *J Hepatol*. 2002;36(suppl):631A.
120. Lo GH, Chen WC, Chen MH, et al. Banding ligation versus nadolol and isosorbide mononitrate for the prevention of esophageal variceal re-bleeding. *Gastroenterology*. 2002;123:728-34.
121. Villanueva C, Minana J, Ortiz J, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med*. 2001;345:647-55.
122. Thalheimer U, Mela M, Patch D, et al. Monitoring target reduction in hepatic venous pressure gradient during pharmacological therapy of portal hypertension: a close look at the evidence. *Gut*. 2004;53:143-8.
123. Vinel JP, Lamouliatte H, Cales P, et al. Propranolol reduces the re-bleeding rate during endoscopic sclerotherapy before variceal obliteration. *Gastroenterology*. 1992;102:1760-3. [Erratum, *Gastroenterology* 1992;103:359.]
124. Avgerinos A, Rekoumis G, Klonis C, et al. Propranolol in the prevention of recurrent upper gastrointestinal bleeding in patients with cirrhosis undergoing endoscopic sclerotherapy: a randomised controlled trial. *J Hepatol*. 1993;19:301-11.
125. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal re-bleeding: a prospective, randomised trial. *Hepatology*. 2000;32:461-5.
126. Burroughs AK, Vangeli M. Transjugular intrahepatic portosystemic shunt versus endoscopic therapy: randomised trials for secondary prophylaxis of variceal bleeding: an updated meta-analysis. *Scand J Gastroenterol*. 2002;37:249-52.
127. Sanyal AJ, Freedman AM, Luketic VA, et al. Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage: a randomised, controlled trial. *Ann Intern Med*. 1997;126:849-57.
128. Jalan R, Forrest EH, Stanley AJ, et al. A randomised trial comparing transjugular intrahepatic portosystemic shunt with variceal band ligation in the prevention of re-bleeding from esophageal varices. *Hepatology*. 1997;26:1115-22.
129. Rossle M, Deibert P, Haag K, et al. Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal re-bleeding. *Lancet*. 1997;349:1043-9.
130. Rossle M, Piotraschke J. Transjugular intrahepatic portosystemic shunt and hepatic encephalopathy. *Dig Dis*. 1996;14(Suppl 1):12-9.
131. Sanyal AJ, Freedman AM, Shiffman ML, et al. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology*. 1994;20:46-55.

132. Chalasani N, Clark WS, Martin LG, et al. Determinants of mortality in patients with advanced cirrhosis after transjugular intrahepatic portosystemic shunting. *Gastroenterology*. 2000;118:138-44.
133. Jabbour N, Zajko AB, Orons PD, et al. Transjugular intrahepatic portosystemic shunt in patients with end-stage liver disease: results in 85 patients. *Liver Transpl Surg*. 1996;2:139-47.
134. Jalan R, Elton RA, Redhead DN, et al. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal re-bleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol*. 1995;23:123-8.
135. Escorsell A, Banares R, Garcia-Pagan JC, et al. TIPS versus drug therapy in preventing variceal re-bleeding in advanced cirrhosis: a randomised controlled trial. *Hepatology*. 2002;35:385-92.
136. Orozco H, Mercado MA, Chan C, et al. A comparative study of the elective treatment of variceal hemorrhage with beta-blockers, transendoscopic sclerotherapy, and surgery: a prospective, controlled, and randomised trial during 10 years. *Ann Surg*. 2000;232:216-9.
137. Shah SR. The difficulties in carrying out this study comparing three established modalities of preventing recurrent variceal hemorrhage in patients with portal hypertension. *Ann Surg*. 2001;234:263-5.
138. Spina GP, Henderson JM, Rikkers LF, et al. Distal spleno-renal shunt versus endoscopic sclerotherapy in the prevention of variceal re-bleeding. A meta-analysis of 4 randomised clinical trials. *J Hepatol*. 1992;16:338-45.
139. Rikkers LF, Jin G, Burnett DA, et al. Shunt surgery versus endoscopic sclerotherapy for variceal hemorrhage: late results of a randomised trial. *Am J Surg*. 1993;165:27-32.
140. Henderson JM, Nagle A, Curtas S, et al. Surgical shunts and TIPS for variceal decompression in the 1990s. *Surgery*. 2000;128:540-7.
141. Orozco H, Mercado MA. The evolution of portal hypertension surgery: lessons from 1000 operations and 50 Years' experience. *Arch Surg*. 2000;135:1389-93.
142. Rosemurgy AS, Serafini FM, Zweibel BR, et al. Transjugular intrahepatic portosystemic shunt vs. small-diameter prosthetic H-graft portacaval shunt: extended follow-up of an expanded randomised prospective trial. *J Gastrointest Surg*. 2000;4:589-97.
143. Rosemurgy AS, Bloomston M, Zervos EE, et al. Transjugular intrahepatic portosystemic shunt versus H-graft portacaval shunt in the management of bleeding varices: a cost-benefit analysis. *Surgery*. 1997;122:794-9.
144. Rosch J, Keller FS. Transjugular intrahepatic portosystemic shunt: present status, comparison with endoscopic therapy and shunt surgery, and future prospectives. *World J Surg*. 2001;25(3):337-45.
145. Huang YH, Yeh HZ, Chen GH, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. *Gastrointest Endosc*. 2000;52:160-7.
146. Lee YT, Chan FK, Ng EK, et al. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc*. 2000;52:168-74.
147. Kind R, Guglielmi A, Rodella L, et al. Bucrylate treatment of bleeding gastric varices: 12 years' experience. *Endoscopy*. 2000;32:512-9.
148. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomised trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*. 2001;33:1060-4.
149. Sarin SK, Jain AK, Jain M, et al. A randomised controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol*. 2002;97:1010-5.
150. Mastumoto A, Matsumoto H, Inokuchi H. Isolated gastric fundal varices: a challenging issue. *Am J Gastroenterol*. 2002;97:2930-1.
151. Chau TN, Patch D, Chan YW, et al. "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology*. 1998;114:981-7.
152. Stanley AJ, Jalan R, Ireland HM, et al. A comparison between gastric and oesophageal variceal haemorrhage treated with transjugular intrahepatic portosystemic stent shunt (TIPSS). *Aliment Pharmacol Ther*. 1997;11(1):171-6.

ACKNOWLEDGEMENT

The committee for this guideline would like to express their gratitude and appreciation to the following for their contribution:

- Panel of reviewers who reviewed the draft
- Technical Advisory Committee for Clinical Practice Guidelines for their valuable input and feedback

DISCLOSURE STATEMENT

The panel members have no potential conflict of interest to disclose.

SOURCES OF FUNDING

The development of this CPG was supported financially in its entirety by the Malaysian Society of Gastroenterology and Hepatology without any involvement of the pharmaceutical industry.

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