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Management of Acute Variceal Haemorrhage and Prevention of Rebleeding

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INTRODUCTION

Acute variceal bleeding accounts for just over 10% of all causes of upper gastrointestinal bleeding presenting to hospital, with two-thirds of these patients having a history of previous variceal bleeding [1]. It is a medical emergency associated with 10-20% mortality within 6 weeks. However, recent improvements in outcome following variceal haemorrhage have been reported and several important guidelines on management have been published [2-4]. This chapter aims to provide an overview of an evidenced based approach to management of acute oesophageal and gastric variceal haemorrhage and in addition, the prevention of rebleeding.

PATHOPHYSIOLOGY, PREVALENCE AND NATURAL HISTORY OF VARICES

Portal hypertension in cirrhosis develops as a result of increasing pressure in the portal circulation secondary to increased hepatic resistance and increased portal blood flow. The Hepatic Venous Pressure Gradient **(HVPG)** is usually between 1-5mmHg and once this figure rises >10mmHg, varices can develop [5].Once the HVPG is ≥12mmHg, variceal bleeding can occur. Similarly, once the HVPG is reduced below 12mmHg (by pharmacological means or after abstinence from alcohol), variceal bleeding is unlikely [6,7]. The prevalence of varices in patients with cirrhosis ranges from 44-53% at 10 and 20 years respectively post diagnosis [8]. Most variceal bleeding arises from oesophageal varices, although 10-20% originate from a gastric variceal source, with a small number from ectopic sources including duodenal and rectal varices.

DEFINITIONS

Variceal haemorrhage is defined as visualised bleeding or stigmata of recent bleeding (Figure. 1) from oesophageal or gastric varices during endoscopy, orthe detection of varices with concurrent gastric blood in the absence of another recognisable cause of bleeding. The acute bleeding episode is defined by the intervalfrom admission with bleeding (time zero) until 120 hours (5 days). Rebleeding is defined as bleeding which occurs after this 5-dayinterval [3].

Acute variceal haemorrhage is clinically significant where there is evidence of haemodynamic compromise defined as: ≥2 unit blood transfusion requirement coupled with a systolic blood pressure <100 mmHg or postural change of >20mmHg and/or heart rate >100bpm at time zero [3]. Variceal rebleeding is clinically significant where there is recurrent haematemesis or melaena in the presence of any or all of: a hospital admission, need for blood transfusion, 30g/L drop in haemoglobin and/or early mortality (death within 6 weeks) [3].

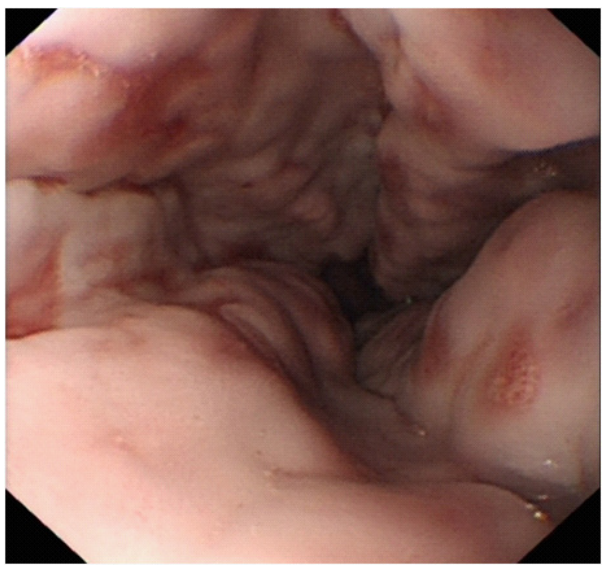

Figure 1: Grade 2 oesophageal varices with "red spots" indicative of recent bleeding.

ORGANISATION OF PATIENT CARE

Units seeing 330 cases a year should implement a daily endoscopy "bleeders" list with the additional of provision of 24/7 cover for those patients who may require more urgent intervention [2]. Expertise in endoscopic variceal band ligation, injection therapy for gastric variceal bleeding (see below) and placement of balloon tamponade are requirements for both the endoscopist and supporting staff. Units seeing less than 330 cases a year should arrange clear referral and/or transfer pathways for their patients via regional agreements.

INITIAL ASSESSMENT OF THE PATIENT WITH SUSPECTED VARICEAL HAEMORRHAGE

A patient with known or suspected chronic liver disease who presents with symptoms or signs of upper gastrointestinal bleeding should be suspected of having variceal haemorrhage. Initial urgent assessment of haemodynamic status and oxygen saturation is essential. Where possible, a detailed history and examination should be taken including elicitation of comorbidities, previous or currentvarices, and signs of liver decompensation. Mortality rates may be doubled byolder age, comorbidities, male gender and endoscopy undertaken >24 hours after presentation [3].

Assessment of signs of sepsis should also be made as concurrent infection carries significant mortality. Pneumonia must be actively excluded and any ascites should be tapped and sent for neutrophil count and culture. Blood and urine should also be cultured. Blood analysis should include full blood count, coagulation profile, renal function, liver function and full cross-match.

Commonly used risk scores for upper GI bleeding, such as the Glasgow Blatchford, admission Rock all or AIMS65 scores, are less accurate for patients with suspected variceal bleeding, as all such patients are immediately at "high risk". However, the Childs-Pugh and MELD score are good predictors of mortality.

Given the high mortality of variceal haemorrhage and concurrent presence of liver disease,the ideal setting for patient management is a high-dependency unit or properly staffed gastrointestinal bleeding unit. Patients with persistent haematemesis, encephalopathy and/or haemodynamically instability should are intubated prior to endoscopy.

PRE-ENDOSCOPIC THERAPYFOR SUSPECTED VARICEAL BLEEDING

Volume Resuscitation and Blood Transfusion

Two 16-18G cannulas should be inserted on admission, with consideration of central venous access given to those patients with poor peripheral access, advanced liver disease or hepatorenal syndrome. Intravenous fluid plasma expanders should be initiated with the aim of maintaining systolic blood pressure around 100mmHg.

A restrictive transfusion policy is recommended [1] with the target haemoglobin level between 70 and 80 g/L. Over transfusion has been shown to have a damaging effect on outcome, as increases in hepatic venousportal gradient may provoke further uncontrolled bleeding [9].

Clotting Factors

The coagulation cascade in patients with chronic liver disease is complex, with patients often having proportionate deficiencies in both procoagulant and anticoagulant factors [10]. Prolonged prothromb in time seen on coagulation profile does not necessarily reflect *in-vivo* coagulation status and is therefore relatively unreliable. The hospital based major haemorrhage protocol should be activated for clinically unstable patients. Use of platelet infusion when platelet count <50, fresh frozen plasma when fibrinogen level <1 or prothrombin/activated partial thromboplastin time >1.5 times upper limit of normal, and prothrombin complex concentrate for patients on warfarin who are actively bleeding are recommended [2]. There is no clear evidence supporting the use of transexamic acid or recombinant factor VIIa [11].

Antibiotics

Prophylactic antibiotics improve outcome in variceal haemorrhage, having been shown to reduce mortality and early rebleeding in addition to reducing bacterial infections [12]. Therefore, standard practice includes the administration of antibiotics to all cirrhotic patients who present with upper gastrointestinal bleeding. The antibiotic of choice should be guided by local resistance patterns with gram-negative cover being essential. Intravenous ceftriaxone 1g/24h should be considered in hospital settings where quinolone resistance is high and for patients on prior quinolone prophylaxis [4].

Vasoconstrictors

Vasoconstrictors should be given as soon as variceal bleeding is suspected, unless there are clear contraindications such as known ischaemic heart disease. The two major pharmacological classes of drugs used are vasopressin analogues, and somatostatin plus its analogues. Vasopressin itself is no longer used due to its high incidence of serious side effects.

Terlipressin, a synthetic analogue of vasopressin, has an immediate vasoconstrictor action followed by portal haemodynamic effects due to its later conversion to vasopressin. Terlipressin has been shown to improve control of bleeding and also improve survival [13]. The recommended dosage is 2mg intravenously every 4 hours however, it may be reduced to 6 hourly if side effects are problematic. Side effects include increased peripheral resistance, reduction in cardiac output and reduction in coronary blood flow, bradycardia and painful extremities secondary to peripheral vasoconstriction. Hyponatraemia has also been observed therefore sodium levels should be monitored. Terlipressin can be continued for up to 5 days, although should be discontinued when satisfactory haemostasis has been achieved [14]. In patients intolerant of Terlipressin or in centres where it is not available, alternative vasoconstrictor therapy should be considered.

Somatostatin causes selective splanchnic vasoconstriction and reducesportal pressure and blood flow but the mechanism of action remains unclear [15].It has a transient action on hepatic and systemic haemodynamics therefore a continuous infusion should be used. Common dosing is an intravenous bolus of 250 micrograms followed by an infusion of 250 micrograms/hour. Octreotide is asomatostatin analogue that may be used when Terlipressin or Somatostatin is unavailable. Octreotide is usually given as an intravenous bolus of 50 micrograms, followed by an infusion of 25-50 micrograms/hour. Somatostatin and Octreotide are as effective as Terlipressin in acute variceal bleeding [16,17].

Proton Pump Inhibitors (PPI)

There is no evidence to suggest that oral or intravenous administration of proton pump inhibitors in patients presenting with variceal haemorrhage improves outcome [18]. Infact, PPI have been shown to increase the incidence of C.Difficile infection [19] and may be linked to increased incidence of Spontaneous Bacterial Peritonitis in cirrhotic patients [20], therefore their use is not recommended.

TIMING OF ENDOSCOPY

All patients with suspected variceal bleeding should have endoscopy performed within 24 hours of presentation. There is no clear evidence that performing endoscopy within 12 hours improves outcome [21]. However, patients with haemodynamic instability, particularly those with advanced liver disease, other comorbidities and older age, should have endoscopy preformed immediately after resuscitation.

ACUTE OESOPHAGEAL VARICEAL BLEEDING

Endoscopic Therapy

Variceal band ligation (VBL)

Variceal band ligation of oesophageal varices is the endoscopic treatment of choice. It has replaced sclerotherapy given thereduced mortality and a lower incidence of oesophageal strictures [22].

Others

Cyanoacrylate offers no benefit over variceal band ligation for oesophageal variceal bleeding and has associated risks of embolisation and increased rebleeding [23]. The evidence for the use of haemostatic powders in acute oesophageal variceal bleeding is currently limited to case reports or small case series [24].

Failure of Endoscopic Therapy

Balloon tamponade

Balloon tamponade using a Sengstaken-Blackmore or Linton tube should only be used to control refractory oesophageal variceal haemorrhage as a bridge to other treatment modalities. The gastric balloon is first inflated with approximately 300mls air and traction applied. Only if this fails to control haemorrhage should the oesophageal balloon be (temporarily) inflated. Although a potential life-saving measure, balloon tamponade can be associated with severe adverse events including aspiration pneumonia, oesophageal ulceration and rebleeding on balloon deflation [25]. Complications may be reduced by placement via guide wire or under directvisualisation atendoscopy. The balloon should be *in situ* no longer than 24-48 hours [26].

Stenting

Self-expanding removable metal mesh oesophageal stents can be placed endoscopically in the lower oesophagus. Early data suggests they may be as efficacious as balloon tamponadeand can be left *in situ* for up to 2 weeks. More data on this modality are required to clarify its role in the management of refractory bleeding.

Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS)

Persistent bleeding despite combined endoscopic and pharmacological treatment is best managed with a poly Tetra Fluro Ethalene **(PTFE)** covered TIPSS. The change in practice from a bare metal stent is supported by evidence that shows PTFE-covered stents have higher primary patency rates than their bare metal counterparts, without any differences in survival. There is also evidence suggesting reduced incidence of hepatic encephalopathy with covered stents [27,28].

Studies observing the outcome of TIPSS insertion as a salvage procedure for variceal bleeding refractory to endoscopic therapy show that control of bleeding was observed in 90-100% of cases, with rebleeding rates of 6-16% [29]. However, the standard endoscopic practice in these studies was sclerotherapy and bare stents were used, therefore management was not in keeping with current best practice.

Units that do not offer TIPSS on-site should have an agreed referral pathway to a regional centre where the procedure can be undertaken after safe transfer of the patient.

Surgery

In cirrhotic patients with variceal haemorrhage, emergency portocaval surgery within 24 hours of presentation has been reported to have better results for long-term bleeding control, encephalopathy and survival when compared with bare metal TIPSS, although procedure related complications are higher [30]. Although studies are needed to compare emergency surgery with PTFE-covered stents for refractory variceal bleeding, the relatively limited availability of surgeons skilled in such procedures means that emergency porto-caval surgery is rarely undertaken in most centres.

PREVENTION OF REBLEEDINGFROM OESOPHAGEAL VARICES

Combination therapy of repeated VBL and Non-cardio Selective Beta-Blockers **(NSBBs)** is the treatment of choice for secondary prophylaxis of oesophageal variceal rebleeding. Studies suggest reduced rebleeding and improved survival with combination therapy (VBL + NSBB) compared with monotherapy of either [31-34]. However, there is some suggestion that adding NSBB to VBL alone improves survival, which may not be the case when adding VBL to NSBB alone. This may be due to the beneficial pleiotropic effect of NSBB in cirrhosis, although further studies assessing this are awaited. In patients with contraindication to or intolerance of NSBB, VBL monotherapy should be used. Similarly, for patients intolerant to VBL, NSBB monotherapy can be administered [4].

Endoscopic Therapy

Variceal band ligation is the endoscopic method of choice for the prevention of rebleeding of oesophageal varices; exhibiting lower rates of rebleeding, mortality and complications than sclerotherapy [35,36]. There is also no evidence that the addition of sclerotherapy to variceal band ligation improves clinically relevant outcomes and also has the disadvantage of increased rates of oesophageal stricture [37,38]. Varices should be banded every 2-4 weeks until eradication is achieved. Thereafter, patients should undergo endoscopy at 3 months and then 6 monthly. Identification of recurrent varices should be treated with repeat band ligation as per the above intervalsuntil eradication is achieved.

Non-selective Beta-Blockers (NSBB)

NSBBs at doses of Propranolol 40-80mg twice a day, Nadalol 80mg per day and Carvedilol 6.25-12.5mg per day have all been suggested for use and should be commenced following control of the acute bleeding episode. Propranolol reduces hepatic venous portal gradient by 10-12% leading to a reduction in bleeding and hepatic decompensation [39,40]. Nadalol appears to have slightly less pronounced effects on blood pressure than Propranolol. Carvedilol also has some alpha-1 receptor antagonistic effects thereby reducing intrahepatic resistance. Studies indicate Carvedilol gives rise to greater reductions in portal pressure compared to Propranolol although hypotension may be an adverse effect [41,42]. At the doses recommended above, Carvedilol is currently the cheapest drug therapy for portal hypertension in the United Kingdom.

Simvastatin

Simvastatin is known to have positive effects on hepatocellular function, fibrosis and portal pressure. The addition of Simvastatin to combined therapy (VBL + NSBB) showed no reduction in rates of rebleeding but did improve mortality in a small-randomised control trial [43]. More studies are required to assess the role of Simvastatin in the prevention of variceal rebleeding before it can be widely recommended.

TIPSS

As discussed above, emergency TIPSS has a role in uncontrolled oesophageal variceal bleeding. However, it is also recommended that TIPSS placement using PTFE-covered stents should be used for the prevention of rebleeding for those patients whom endoscopic and pharmacological prevention of rebleeding fails [1]. Although studies have reported higher rates of hepatic encephalopathy in TIPSS patients, many of these studies assessed bare metal stents only [44].

Early insertion of PTFE-covered TIPSS within 72 hours should be considered in patients bleeding from oesophageal varices who are at high risk of treatment failure, including those with Child-Pugh class C <14 points or Child-Pugh class B with active bleeding, after initial control using endoscopic and pharmacological therapy [1].This subgroup has shown improved survival when early TIPSS is placed [45].

Another study suggested that early insertion of bare TIPSS post successful endoscopic therapy in patients with a hepatic venous portal gradient >20mmHg significantly improves control of bleeding, reduces rates of rebleeding and improves survival [46]. However, the comparisons were between sclera therapy and bare metal stents, therefore not consistent with current best practice. More studies assessing the use of early TIPSS post-endoscopic therapy are needed.

Surgery

In Childs A or B patients whom TIPSS is not possible, portosystemics hunt surgery could be considered if local resources and expertise allow.

MANAGEMENT OF REBLEEDINGFROM OESOPHAGEAL VARICES

Rebleeding may be managed by repeat endoscopic therapy using VBL. However, PTFE-covered TIPSS may also be used for patients who rebleed, particularly in cases of severe rebleeding or repeated rebleeding despite the measures described above [4].

Below, we show a summary algorithm (Figure. 2) for the management of oesophageal variceal bleeding. The figure has been adapted from reference 4.

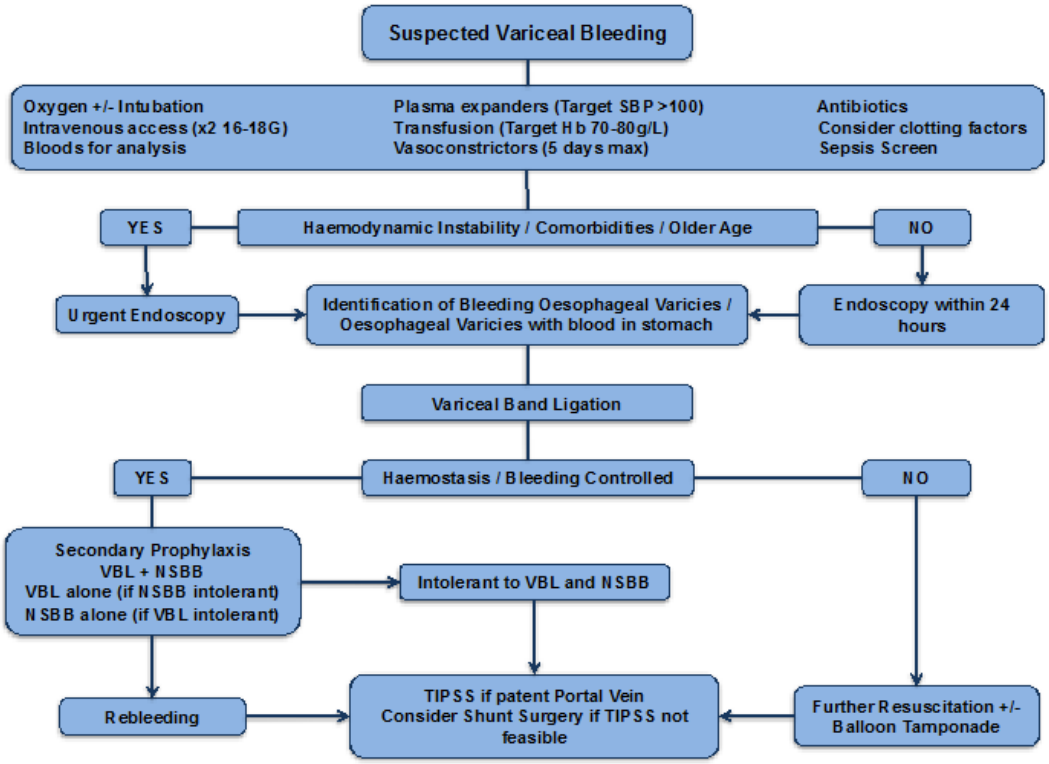

Figure 2: Management of oesophageal variceal bleeding.

ACUTE GASTRIC VARICEAL BLEEDING

Although gastric variceal bleeding is much less common than bleeding from oesophageal varices, bleeding can be more severe and management more challenging. Gastric varices are classified due to their anatomical location using the Sarin classification [47]. Gastro-Oesophageal Varices **(GOV)** are an extension of oesophageal varices with GOV-1 extending 2-5cm below the oesophageal-gastric junction along the lesser curve of the stomach, whereas GOV-2 extends into the fundus. Isolated Gastric Varices **(IGV)** occur independently of oesophageal varices. IGV-1 occurs only in the fundus, whereas IGV-2 occurs in the body, antrum or pylorus. Of the above, GOV-1 are the most common whereas IGVs are associated with worse outcome [48]. It is important to identify which varices are seen at endoscopy as their classification has implications for management.

Endoscopic Therapy

Variceal Band Ligation

As previously mentioned, VBL has replaced the use of sclera therapy. However, the only role for standard VBL (or use of detachable loop snares) is in the treatment of bleeding GOV-1 as they

are managed as extensions of oesophageal varices. VBL is not recommended for other types of gastric varices asrebleeding rates are high due to their larger size and vascular anatomy [49,50].

Endoscopic injection of Cyanoacrylate (Figure. 3)

Numerous cohort and some randomised studies have reported the use of endoscopic injection of tissue adhesives such as cyanoacrylate in the treatment of gastric variceal haemorrhage. Although there are serious potential complications such as distant embolization of glue, cyanoacrylate injection has been shown to lead to lower rebleeding and higher or equal haemostasis and survival rates when compared to VBL [51-53]. Cyanoacrylate injection was shown to lead to significantly higher haemostasis and survival rates after gastric variceal bleeding compared with sclerotherapy [54].

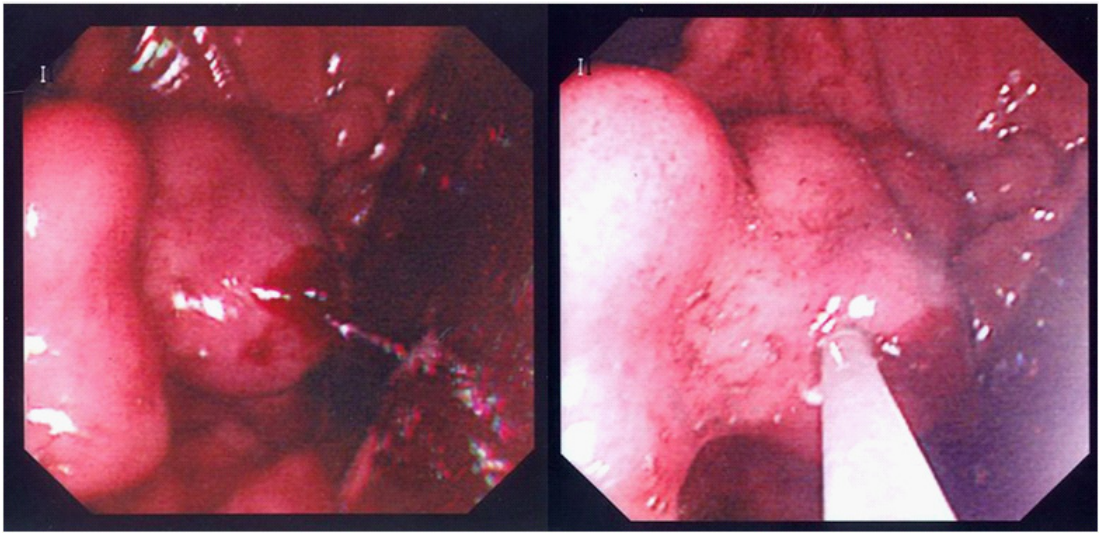

Figure 3: Acute gastric variceal bleeding (left) with injection of cyanoacrylate (right).

Although VBL remains the mainstay of treatment of GOV-1, endoscopic injection of cyanoacrylate is thereforethe recommended endoscopic treatment for GOV-2, IGV-1 and IGV-2 [4].

Endoscopic injection of thrombin

Endoscopic injection of bovine thrombin to bleeding gastric varices has been shown to successfully control acute bleeding, however there are obvious safety concerns with the use of bovine products. Injection of human thrombin has been studied more recently with publications reporting high rates of initial haemostas is but rebleeding rates up to 50%during follow-up [55]. However to date, no randomised studies of thrombin injection exist. Therefore, human thrombin injection should generally be considered only if cyanoacrylate is unavailable.

Failure of Primary Endoscopic Therapy

Balloon tamponade

Similar to refractory oesophageal variceal bleeding, Sengstaken-Blackmore or Linton tube insertion may be used to temporarily stabilise the patient who is bleeding from GOV-1, GOV-2 and IGV-1 until more definite measures are undertaken [56].

TIPSS

Salvage TIPSS is indicated when all primary endoscopic methods fail. Bare metal stents control active bleeding from gastric varices when the shunt can be successfully placed [57-61]. However, assessment of portal and splenic vein patency should be undertaken prior to TIPSS procedure, as thrombosis of these veins is a recognised predisposition to the development of gastric varices. Similar to oesophageal variceal bleeding, PTFE-covered stents should now be used due to their improved patency rates [3,4].

Balloon-occluded retrograde transvenous obliteration (B-RTO)

B-RTO involves the insertion of a balloon catheter via the femoral or internal jugular vein into a gastrorenal or gastric-inferior vena caval outflow shunt. Inflation of the balloon inhibits blood flow allowing subsequent micro-coil embolisation of veins draining the varices and variceal eradication with subsequent sclerosant injection [62,63]. Several studies report good success rates of B-RTO in achieving haemostasis in gastric variceal bleeding, however there is a risk of increased portal pressure gradient, which may aggravate pre-existing oesophageal varices or ascites. B-RTO compared with TIPSS had similar rates of haemostasis, rebleeding and encephalopathy [64].

In patients who have uncontrolled bleeding from gastric varices, B-RTO can be used as an alternative therapy where TIPSS is unavailable provided shunts are appropriate. However, to date B-RTO is rarely used outside Asia.

Surgery

In the absence of the above measures, portosystemic shunt surgery should be considered depending on local resources and expertise.

PREVENTION OF REBLEEDING FROM GASTRIC VARICES

Variceal band ligation

Patients with GOV-1 should be entered into a VBL eradication and surveillance program similar to patients who presented with oesophageal variceal bleeding (see above).

Endoscopic injection of cyanoacrylate

As mentioned above, cyanoacrylate injection therapy can have equal or better rates of rebleeding compared to the use of VBL for gastric varices. Additionally, cyanoacrylate also

hasimproved rates of rebleeding and survival compared to use of beta-blockers [65]. Patients should be entered into an endoscopic surveillance programme with the injection of cyanoacrylate into GOV-2, IGV-1 and IGV-2. Optimum timing of endoscopic follow up remains unclear.

TIPSS

TIPSS should be used if patients rebleed despite cyanoacrylate (or thrombin) injection or if patients have multiple large gastric varices including a "bunch of grapes" appearance in the fundus [66]. Early TIPSS should be considered in patients who presented with gastric variceal haemorrhage from GOV1 or GOV2 with high risk of treatment failure e.g. Child Pugh class C<14 or Child-Pugh class B with active bleeding after initial pharmacological and endoscopic therapy [3].

NSBBs

When repeat endoscopy is inappropriate and other secondary prophylactic measures are unavailable or unsuitable, patients should be considered for NSBB therapy in doses similar to those described above for prevention of oesophageal variceal rebleeding.

Surgery

The need and availability of skills required forsurgical intervention has reduced given the availability and success of the measures outlined above. However, there remains a potential role for surgery in patients who have had bled from gastric varices secondary to splenic vein thrombosis. These patients should be considered for splenectomy or embolisation of the splenic artery [67,68].

CONCLUSION

Early identification of the patient with suspected variceal bleeding is important, with management carried out in an appropriate setting. Effective pre-endoscopic treatment provides a platform for improved outcome prior to the diagnosis and subsequent treatment of bleeding oesophageal or gastric varices. The endoscopic therapy of choice for oesophageal varices (and GOV1) is variceal band ligation, whereas gastric varices (GOV2 & IGVs) should be treated with cyanoacrylate injection.

Secondary prophylaxis and the prevention of rebleeding of oesophageal varices (and GOV1) is optimally managed with combination therapy of VBL and NSBB. Gastric varices should have further injection with cyanoacrylate.

TIPSS remains a therapeutic option for management of acute bleeding refractory to endoscopic therapy, rebleeding and the prophylaxis of further variceal haemorrhage. In selected patients and certain centres, porto-caval surgery may be performed.

Improvements in endoscopic, pharmacological and radiological therapies for the management of variceal bleeding, backed up by publication of many recent studies and guidelines in this area, have led to improvements in outcomes. However, there is plenty of scope for further studies to investigate the role of novel treatments to, perhaps, lead to further continued improvement.

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