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UK guidelines on the management of variceal haemorrhage in cirrhotic patients

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ABSTRACT

These updated guidelines on the management of variceal haemorrhage have been commissioned by the Clinical Services and Standards Committee (CSSC) of the British Society of Gastroenterology (BSG) under the auspices of the liver section of the BSG. The original guidelines which this document supersedes were written in 2000 and have undergone extensive revision by 13 members of the Guidelines Development Group (GDG). The GDG comprises elected members of the BSG liver section, representation from British Association for the Study of the Liver (BASL) and Liver QuEST, a nursing representative and a patient representative. The quality of evidence and grading of recommendations was appraised using the AGREE II tool.

The nature of variceal haemorrhage in cirrhotic patients with its complex range of complications makes rigid guidelines inappropriate. These guidelines deal specifically with the management of varices in patients with cirrhosis under the following subheadings: (1) primary prophylaxis; (2) acute variceal haemorrhage; (3) secondary prophylaxis of variceal haemorrhage; and (4) gastric varices. They are not designed to deal with (1) the management of the underlying liver disease; (2) the management of variceal haemorrhage in children; or (3) variceal haemorrhage from other aetiological conditions.

Summary of all recommendations

Recommendations: primary prophylaxis of variceal haemorrhage in cirrhosis (Figure 2)

1. What is the best method for primary prophylaxis?
   1.1. We recommend non-cardioselective β blockers (NSBB) or variceal band ligation (VBL). We suggest pharmacological treatment with propranolol as first line. VBL is offered if there are contraindications to NSBB. The choice of VBL or NSBB should also take into account patient choice (level 1a, grade A).
   1.2. We suggest carvedilol or nadolol as alternatives to propranolol (level 1b, grade A).
   1.3. Dose:
      1.3.1. Propranolol: 40 mg twice daily. Dose titrated to maximum tolerated or once heart rate (HR) of 50–55 bpm is reached to a maximum dose of 320 mg (level 1a, grade A).
      1.3.2. Nadolol: 40 mg daily dose. Dose titrated to maximum tolerated or once HR of 50–55 bpm is reached a maximum dose of 240 mg (level 1a, grade A).
      1.3.3. Carvedilol: 6.25 mg once daily to increase to maintenance of 12.5 mg after a week if tolerated or once HR of <50–55 bpm is reached (level 1a, grade A).
      1.3.4. It is suggested that NSBB are discontinued at the time of spontaneous bacterial peritonitis, renal impairment and hypotension (level 2b, grade B).
   1.4. In cases of contraindications or intolerance to NSBB, we recommend variceal band ligation (level 1a, grade A).
2. Who should have surveillance for variceal bleeding?
   2.1. We recommend all patients with cirrhosis should be endoscoped at the time of diagnosis (level 1a, grade A). There is no indication to repeat endoscopy in patients receiving NSBB.
3. How often should cirrhotic patients be endoscoped?
   3.1. If at the time of first endoscopy no varices are seen, we suggest that patients with cirrhosis should be endoscoped at 2–3-year intervals (level 2a, grade B).
   3.2. If grade I varices are diagnosed, we suggest that patients should be endoscoped at yearly intervals (level 2a, grade B).
   3.3. If there is clear evidence of disease progression we suggest that the intervals can be modified by the clinician. Endoscopy should also be offered at time of decompensation (level 2a, grade B).
4. Which patients with cirrhosis should have primary prophylaxis?
   4.1. If grade I varices and red signs or grade 2–3 varices are diagnosed, we recommend that patients have primary prophylaxis irrespective of the severity of the liver disease (level 1a, grade A).
5. Treatments not recommended:
   5.1. Proton pump inhibitors are not recommended unless otherwise required for peptic ulcer disease (level 1b, grade B).
   5.2. Isosorbide mononitrate monotherapy is not recommended as primary prophylaxis (level 1b, grade A). There is insufficient evidence to recommend isosorbide mononitrate in combination with NSBB (level 1b, grade A).

5.3. Shunt surgery or transjugular intrahepatic portosystemic stent shunt (TIPSS) is not recommended as primary prophylaxis (level 1a, grade A).

5.4. Sclerotherapy is not recommended as primary prophylaxis (level 1a, grade A).

6. Areas requiring further study:

6.1. Role of NSBB in patients without varices, with focus on carvedilol.

6.2. Role of NSBB in patients with small varices, with focus on carvedilol.

6.3. Comparison of carvedilol versus propranolol in primary prophylaxis.

6.4. Identification of, and trials assessing, new drugs for primary prophylaxis such as statins.

7. Quality indicator:

7.1. Percentage of patients at diagnosis of cirrhosis who have had an endoscopy to screen for varices (level 1a, grade A).

Numerator; patients diagnosed with cirrhosis who have had an endoscopy either before or after diagnosis within 6 months.

Denominator; patients newly diagnosed with cirrhosis.

7.2. Percentage of patients receiving primary prophylaxis among those newly diagnosed with grade I varices and red signs or grade 2–3 varices.

Numerator; patients who have grade 1 varices with red signs or grade 2–3 varices receiving primary prophylaxis.

Denominator; patients diagnosed with cirrhosis who have grade I varices with red signs or grade 2–3 varices.

Recommendations: control of active variceal haemorrhage in cirrhosis (Figure 3)

1. Suggestions for resuscitation and initial management

1.1. Units offering an emergency acute upper gastrointestinal bleeding service should have expertise in VBL, balloon tamponade and management of gastric variceal bleeding (level 5, grade D).

1.2. Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding (level 5, grade D).

1.3. Base decisions on blood transfusion on the full clinical picture, recognising that overtransfusion may be as damaging as undertransfusion. A restrictive transfusion policy aiming for a haemoglobin of 70–80 g/L is suggested in haemodynamically stable patients (level 1b, grade B).

1.4. Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable (level 5, grade D).

1.5. Offer platelet transfusion to patients who are actively bleeding and have a platelet count of $<50\times10^9$/L (level 5, grade D).

1.6. Offer fresh frozen plasma to patients who have either:
▶ a fibrinogen level of <1 g/L (level 5, grade D), or
▶ a prothrombin time (international normalised ratio) or activated partial thromboplastin time >1.5 times normal (level 5, grade D).

1.7. Offer prothrombin complex concentrate to patients who are taking warfarin and actively bleeding (level 5, grade D).

1.8. Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols (level 5, grade D).

1.9. There is insufficient evidence for the use of recombinant factor VIIa in acute variceal haemorrhage (level 1b, grade B).

2. Suggestions for timing of upper gastrointestinal endoscopy:

2.1. Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation (level 5, grade A).

2.2. Offer endoscopy within 24 h of admission to all other patients with upper gastrointestinal bleeding (level 2b, grade A).

2.3. Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances (level 5, grade D).

3. Control of bleeding:

3.1. Antibiotics are recommended for all patients with suspected or confirmed variceal bleeding (level 1a, grade A).

3.2. In all patients, vasoconstrictors such as terlipressin or somatostatin are recommended and should be started as soon variceal bleeding is suspected and continued until haemostasis is achieved or for up to 5 days. Octreotide (unlicensed) is suggested if terlipressin or somatostatin are unavailable (level 1a, grade A).

3.3. Variceal band ligation is recommended as the preferred endoscopic method (level 1a, grade A).

3.4. After satisfactory haemostasis with the methods above, and depending on local resources, early covered TIPSS (<72 h after index variceal bleed) can be considered in selected patients with Child's B cirrhosis and active bleeding or Child's C cirrhosis with Child's score <14 (level 1b, grade B).

3.5. Proton pump inhibitors are not recommended unless otherwise required for peptic ulcer disease (level 1b, grade B).

4. Failure to control active bleeding:

4.1. If bleeding is difficult to control, a Sengstaken–Blakemore tube should be inserted until further endoscopic treatment, TIPSS or surgery is performed depending on local resources and expertise (level 1b, grade B).

4.2. Specialist help should be sought at this time and transfer to a specialist centre should be considered. Units that do not offer a TIPSS service should identify a specialist centre which offers a 24 h emergency TIPSS service and have appropriate arrangements for safe transfer of patients in place (level 2a, grade B).

5. Areas requiring further study:

5.1. The efficacy of restrictive blood transfusion in variceal haemorrhage.

5.2. The role of blood products in variceal haemorrhage.

5.3. The utility of early TIPSS (<72 h) in acute variceal haemorrhage.

5.4. The role of removable oesophageal stents in acute variceal haemorrhage.

5.5. The role of haemostatic powders in acute variceal haemorrhage.

5.6. The role of proton pump inhibitors in variceal haemorrhage.

6. Quality indicators

6.1. Antibiotic administration in acute variceal bleeding within 1 day either before or after the procedure (level 1a, grade A).

Numerator; patients with an acute variceal bleed who have received antibiotics within 1 day either before or after the procedure.

Denominator; patients with an acute variceal bleed.

6.2. Endoscopy performed within 24 h of presentation of an acute variceal bleed (level 2b, grade A).
Numerator; patients with an acute variceal bleed who have received endoscopy within 24 h of presentation.
Denominator; patients with an acute variceal bleed.

Recommendations: secondary prophylaxis of variceal haemorrhage in cirrhosis (figure 3)

1. Should VBL be used in combination with NSBB?
   1.1. NSBB (propranolol or nadolol)+VBL combination therapy are recommended as secondary prophylaxis (level 1a, grade A).
   1.2. NSBB or VBL monotherapy are suggested as alternative options taking into account patient preference and clinical judgement (level 1a, grade B).
   1.3. Carvedilol is suggested as an alternative to propranolol and nadolol (level 1b, grade B).
   1.4. If NSBB alone are used, there is no need to undertake further endoscopy unless clinically indicated (level 1a, grade A).
   1.5. We recommend that VBL alone is used to eradicate varices if there are contraindications or intolerance to combined use with NSBB (level 1a, grade A).
2. What is the optimal protocol for VBL?
   2.1. It is suggested that varices are banded at 2–4-weekly intervals until eradication (level 1b, grade B).
   2.2. After successful eradication of the varices, patients should be endoscoped at 3 months, then 6 monthly thereafter. Any recurrent varices should be treated with further VBL until eradication (level 1b, grade B).
   2.3. Proton pump inhibitors are not recommended unless otherwise required for peptic disease (level 1b, grade B).
3. When is TIPSS indicated?
   3.1. We suggest that TIPSS is used for patients who rebleed despite combined VBL and NSBB therapy (or when monotherapy with VBL or NSBB is used owing to intolerance or contraindications to combination therapy), and in selected cases owing to patient choice. PTFE-covered stents are recommended (level 1a, grade A).
   3.2. Where TIPSS is not feasible in Child's A and B patients, we suggest shunt surgery can be used where local expertise and resources allow (level 1b, grade B).
4. Areas requiring further study:
   4.1. Combination of VBL and carvedilol (or other NSBB) versus carvedilol as monotherapy.
   4.2. Comparison of carvedilol with propranolol in secondary prophylaxis.
   4.3. Optimum time interval between VBL sessions.
   4.4. Strategy of VBL or NSBB discontinuation after variceal eradication during combination therapy with VBL +NSBB.
   4.5. Strategy of VBL add-on therapy to failure of NSBB monotherapy.
   4.6. Strategy of NSBB add-on therapy to failure of VBL monotherapy.
   4.7. Role of early TIPSS in secondary prophylaxis.
   4.8. Role of statins in secondary prophylaxis.
5. Quality indicator:
   5.1. Institution of secondary prophylaxis after acute variceal bleeding (level 1a, grade A)
   Numerator; patients with an acute variceal bleed who have received either NSBB or banding or both within 4 weeks of the index bleed.
   Denominator; patients with an acute variceal bleed.

Recommendations: management of active haemorrhage from gastric varices (Figure 3)

1. What is the optimal management of bleeding gastro-oesophageal varices?
   1.1. Gastro-oesophageal varices (GOV)-1: treat as for oesophageal varices (level 2b, grade B).
   1.2. GOV-2 and isolated gastric varices (IGV):
      1.2.1. We recommend initial endoscopic therapy with cyanoacrylate injection (level 1a, grade A).
      1.2.2. Thrombin may also be considered (level 4, grade C).
   1.3. TIPSS can be considered, depending on local resources and clinical judgement (level 3a, grade B).
2. If control of bleeding fails:
   2.1. Balloon tamponade is suggested for GOV and IGV-1 until definitive treatment is undertaken (level 2b, grade B).
   2.2. Salvage TIPSS is suggested as the first-line definite treatment, where feasible (level 3a, grade B).
   2.3. Balloon-occluded retrograde transvenous obliteration (B-RTO) or surgical shunting can be considered if TIPSS is not possible (eg, portal vein thrombosis present) and depending on local resources (level 3a, grade B).
3. What are the therapeutic options for prevention of rebleeding from gastric varices?
   3.1. We recommend that patients with GOV-1 are entered into a VBL surveillance programme (level 2b, grade B).
   3.2. We recommend endoscopic surveillance with cyanoacrylate injection as needed for GOV-2 and IGV (level 2b, grade B). Note the optimum endoscopic follow-up strategy remains unclear. Thrombin can also be considered (level 4, grade C).
   3.3. NSBB can be considered in certain circumstances after taking into account the patient's preferences and clinical judgement (level 1b, grade B).
   3.4. We suggest TIPSS if patients rebleed despite cyanoacrylate injection. TIPSS can also be considered in other selected patients (eg, those with large or multiple gastric varices) (level 1b, grade B).
   3.5. Shunt surgery may be used in selected patients with well-compensated cirrhosis and depending on local resources (level 3c, grade B).
   3.6. Splenectomy or splenic artery embolisation should be considered in all patients where there is splenic vein thrombosis or left-sided portal hypertension (level 4, grade C).
4. Is there a role for primary prophylaxis of gastric variceal bleeding?
   4.1. NSBB (level 2a, grade B) can be considered in selected high-risk patients with large GOV-2 after taking into account the patient's preferences and clinical judgement.
   4.2. Cyanoacrylate injection is not recommended outside clinical trials (level 2a, grade A).
5. Areas requiring further study:
   5.1. Role of thrombin in gastric varices, comparing this with tissue adhesives in both acute gastric variceal bleeding and secondary prophylaxis.
   5.2. Role of TIPSS in acute gastric variceal bleeding and secondary prophylaxis.
   5.3. Role of haemostatic powders in controlling refractory active gastric variceal bleeding.
   5.4. Role of NSBB in the prevention of rebleeding from gastric varices.
   5.5. Role of B-RTO as monotherapy or in combination with endoscopic injection of tissue adhesives in prevention of bleeding from gastric varices.

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5.6. Role of endoscopic ultrasound-guided injection of tissue adhesives or thrombin.

5.7. Primary prevention of gastric variceal bleeding with tissues adhesives and NSBB.

INTRODUCTION

The guidelines refer closely to the Baveno V consensus statement published in 2010[1] and the 2012 NICE Guidelines on Acute Upper GI bleeding (CG141).[2] These documents are widely used and offer useful evidence-based guidance. However, we feel that owing to significant recent advances, further additions and refinements to the published guidance, with particular focus on resource implications, service development and the patient pathway, are necessary. The previously mentioned documents[1] [2] do not cover all the recent advances—in particular, in the field of acute variceal bleeding and the role of transjugular intrahepatic portosystemic stent shunt (TIPSS). There have also been developments and better insights into drug treatment for prevention of varices and variceal bleeding—in particular, the role of non-cardioselective β blockers (NSBB).

Guideline development

These guidelines were drafted after discussions within the liver section of the British Society of Gastroenterology (BSG) and acceptance of the proposal by the Clinical Services and Standards Committee (CSSC). There followed division of sections to be researched by designated authors and an exhaustive literature review. The Baveno V consensus and NICE guidelines were closely followed and guideline quality was assessed using the AGREE tool[3] (section 'Assessing the quality of guidelines: the AGREE II instrument').

A preliminary guideline document was drafted by the authors following discussion and, where necessary, voting by members of the Guidelines Development Group (GDG). The draft guidelines were submitted for review by CSSG, then BSG council members. Finally, full peer review was undertaken by reviewers selected by the editor of *Gut*.

Attempts were made to preserve the format of the original guidelines, with additional sections relating to service development, the patient pathway and pre-primary prophylaxis. The section on the management of acute variceal bleeding has been extensively rewritten to take into account recent important developments in interventional radiology, drug treatment and resuscitation.

Assessing the quality of guidelines: the AGREE II instrument

The AGREE II instrument is an accepted method for appraising clinical guidelines.[3] Six domains are listed:

Scope and purpose

The guidelines are intended for use by clinicians and other healthcare professionals managing patients with cirrhosis and gastro-oesophageal varices in light of recent guidance published by NICE[2] and the Baveno V Consensus.[1] Important subsequent developments are covered in depth due to the potential impact on clinical practice. The guidelines are primarily aimed at management of adult patients

Guideline development group membership and stakeholder involvement

Membership of the group includes gastroenterologists, hepatologists and interventional radiologists with nursing and patient representation.

Rigour of development

The published literature was searched using Pubmed, Medline, Web of Knowledge and the Cochrane database between October 2013 and February 2015. The GDG met through a series of teleconferences during that time. The guidelines rely considerably on consensus statements published by the Baveno V Consensus and NICE.[1] [2] The style of graded recommendations is determined by the level of supporting evidence (graded level 1 to 5) as described by the Oxford Centre For Evidence Based Medicine[4] (table 1) and is as follows:

A: consistent level 1 studies;

B: consistent level 2 or 3 studies or extrapolations from level 1 studies;

C: level 4 studies or extrapolations from level 2 or 3 studies;

D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Areas of disagreement about the recommendation grade were subjected to discussion and, if necessary, voting by members of the guidelines group. Where possible, the health benefits, side effects and risks of recommendations have been discussed. The guidelines were subject to peer review after submission for consideration of publication in *Gut*.

Clarity and presentation

Recommendations are intended to be specific to particular situations and patient groups; where necessary, different options are listed. Key recommendations are linked to discussion threads on a discussion forum hosted on the BSG website.

Applicability

Where necessary, we have discussed organisational changes that may be needed in order to apply recommendations. We have attempted to identify key criteria for monitoring and audit purposes.

Editorial independence and conflict of interest

Guideline group members have declared any conflicts of interest.

Scheduled review of guidelines

The proposed time for review of the guidelines is 5 years to take into account new developments. To ensure that there is a facility for feedback after publication, links to the BSG discussion forums corresponding to the particular section of these guidelines are included with this document. This facility to provide new evidence is provided to all BSG members. In accordance with the AGREE II tool the BSG forum will provide feedback.

SERVICE DELIVERY AND DEVELOPMENT

Despite improvements in outcomes following variceal bleeding, the need to optimise the management of acute variceal bleeding is highlighted in recent publications and national reports. In a national audit,[5] variceal bleeding accounted for just over 10% of all admissions with acute GI bleeding in the UK, with two-thirds having a previous history of variceal bleeding and over 50% presenting during normal working hours. Endoscopy within 24 h of presentation was achieved in only 66% of all patients and in 70% of patients with documented cirrhosis. Most procedures were performed in the endoscopy department, with just 14% performed under general anaesthetic despite high-risk stigmata and endoscopic therapy being required in two-thirds of cases. Notably, antibiotics were

Table 1 Levels of evidence

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	DDX/symptom prevalence study
1a	SR (with homogeneity*) of randomised controlled trial (RCT)	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies
1b	Individual RCT (with narrow CI)	Individual inception cohort study with ≥80% follow-up; CDR† validated in a single population	Validating‡ cohort study with good§ reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up¶
1c	All or none**	All or none case series	Absolute SpPins and SnNouts††	All or none case series
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies
2b	Individual cohort study (including low-quality RCT; eg, <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on split sample‡‡ only	Exploratory‡ cohort study with good§ reference standards; CDR† after derivation, or validated only on split sample‡‡ or databases	Retrospective cohort study, or poor follow-up
2c	'Outcomes' research; ecological studies	'Outcomes' research		Ecological studies
3a	SR (with homogeneity*) of case–control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual case–control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study or very limited population
4	Case series (and poor quality cohort and case-control studies§§)	Case series (and poor quality prognostic cohort studies¶¶)	Case–control study, poor or non-independent reference standard	Case series or superseded reference standards
5	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'

*Homogeneity means a systematic review (SR) that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all SRs with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.
†CDR, Clinical Decision Rule (algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category).
‡Validating studies test the quality of a specific diagnostic test based on prior evidence. An exploratory study collects information and trawls the data (eg, using a regression analysis) to find which factors are 'significant'.
§Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
¶Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg, 1–6 months acute, 1–5 years chronic).
**Met when all patients died before the treatment became available but some now survive while receiving it; or when some patients died before the treatment became available but none now die while receiving it.
††An 'absolute SpPin': a diagnostic finding whose Specificity is so high that a Positive result rules in the diagnosis. An 'Absolute SnNout': a diagnostic finding whose Sensitivity is so high that a Negative result rules out the diagnosis.
‡‡Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into 'derivation' and 'validation' samples.
§§Poor quality cohort study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. Poor quality case–control study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
¶¶Poor quality prognostic cohort study: one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded non-objective way, or there was no correction for confounding factors.

administered in only 27% of patients before endoscopy, and administration of vasoactive drugs before endoscopy was only slightly higher at 44%. Furthermore, only four patients (<1%) were referred for TIPSS, which may reflect the lack of access to interventional radiology, and that the audit was conducted before the trial of early TIPSS.[6] The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report 'Measuring the units' assessed clinical management before death of 594 patients with alcoholic liver disease over a 6-month period in the UK.[7] Gastrointestinal bleeding was noted in 35% of cases, with approximately 50% having variceal bleeding. Delays in endoscopy were noted in 10% of cases, and several aspects of clinical and/or organisational care were judged to be poor or unacceptable in 18% of patients presenting with GI bleeding. There were deficiencies noted in the out-of-hours rotas for GI bleeding, with 27% of hospitals not having a dedicated-out-of hours GI bleeding service. Studies from other countries have also reported deficiencies, with delays in admission to hospital and administration of antibiotics. Two observational studies showed that access to emergency endoscopy and use of prophylactic antibiotics and vasoactive drugs was better in tertiary centres, although this did not appear to affect survival.[8 9]

Acute variceal haemorrhage refractory to endoscopic and pharmacological treatments, where TIPSS is usually indicated, must be managed with appropriate resources. TIPSS is an established interventional treatment for refractory or recurrent variceal haemorrhage. It remains a highly specialised procedure, requiring adequate training and experience. Knowledge of the relevant equipment, anatomy and how to deal with any complications is essential. It should therefore be performed in centres with adequate personnel, multidisciplinary support and equipment required to optimise management and minimise risks.[10] Regional centres with easily accessible interventional radiology services are generally best equipped to perform this procedure. Setting up regional agreements and pathways to allow transfer of appropriate patients to hospitals that undertake TIPSS procedures is an important step. These pathways could also be used to provide emergency endoscopic management if necessary due to problems with out-of-hours endoscopic cover in smaller

hospitals. This model referred to as "spoke and wheel" or network model, is well established for other complex procedures and helps to expedite and streamline the process. In the NCEPOD report 'Measuring the units' just 15% of hospitals had on-site access to TIPSS, while 72% had access to TIPSS in other centres.[7]

There have been significant efforts to address the need to improve the upper GI bleeding (UGIB) service. A toolkit was produced in collaboration with BSG; Association of Upper Gastrointestinal Surgeons (AUGIS); Royal Colleges of Physicians, Radiology and Nursing; and Academy of Medical Royal Colleges.[11] The key nine service standards recommended by the document are detailed below:

1. There will be a nominated individual with the authority to ensure implementation by the contracted provider.
2. Contracted providers will ensure the minimum service is adequately resourced.
3. All patients with suspected UGIB should be properly assessed and their risk scored on presentation.
4. All patients should be resuscitated before therapeutic intervention.
5. All high-risk patients with UGIB should be endoscoped within 24 h, preferably on a planned list in the first instance.
6. For patients who require more urgent intervention either for endoscopy, interventional radiology or surgery formal 24/7 arrangements must be available.
7. The necessary team, meeting an agreed competency level, should be available throughout the complete patient pathway.
8. Each stage of the patient pathway should be carried out in an area with 'appropriate' facilities, equipment and support including staff experienced in the management of UGIB.
9. All hospitals must collect a minimum dataset in order to measure service provision against auditable outcomes (case-mix adjusted as appropriate).

NICE recommendations for endoscopy provision are detailed in the section 'Management of active variceal haemorrhage' recommendations.[2] The BSG has also produced a care bundle for patients admitted with decompensated cirrhosis in light of the NCEPOD report with a check list method which includes gastrointestinal bleeding.[12]

Since the 2008 Darzi report, quality has become a priority for the NHS.[13] With these guidelines there is real opportunity to introduce quality outcomes based on good clinical evidence. Furthermore by incorporating them into the liver accreditation scheme, Liver Quest, one can improve and assure quality in liver services across the UK.[14] Therefore a small number of quality outcomes measures have been chosen and form part of the key recommendations.[15]

DEFINITIONS

It is important to define the terms that should be used in the context of a variceal bleed. These are the Baveno V consensus definitions.[1]

Variceal haemorrhage

Variceal haemorrhage is defined as bleeding from an oesophageal or gastric varix at the time of endoscopy or the presence of large oesophageal varices with blood in the stomach and no other recognisable cause of bleeding. An episode of bleeding is clinically significant when there is a transfusion requirement for 2 units of blood or more within 24 h of the time zero, together with a systolic blood pressure of <100 mm Hg or a postural change of >20 mm Hg and/or pulse rate >100 bpm at time

zero (time zero is the time of admission to the first hospital to which the patient is taken).

Time frame of acute bleeding

The acute bleeding episode is represented by an interval of 120 h (5 days) from time zero. Evidence of any bleeding after 120 h is the first rebleeding episode.

Failure to control active bleeding

Failure to control active bleeding is defined as death or need to change treatment defined by one of the following criteria:[16 17]
1. Fresh haematemesis or nasogastric aspiration of ≥100 mL of fresh blood ≥2 h after the start of a specific drug treatment or therapeutic endoscopy.
2. Development of hypovolaemic shock.
3. 30 g/L drop in haemoglobin (9% drop of haematocrit) within any 24 h period if no transfusion is given. This time frame needs to be further validated.

Variceal rebleeding

Variceal rebleeding is defined as the occurrence of a single episode of clinically significant rebleeding from portal hypertensive sources from day 5. Clinically significant rebleeding is defined as recurrent melaena or haematemesis in any of the following settings:
1. hospital admission;
2. blood transfusion;
3. 30 g/L drop in haemoglobin;
4. death within 6 weeks.

Early mortality

Death within 6 weeks of the initial episode of bleeding.

NATURAL HISTORY OF VARICES IN CIRRHOSIS
Development of varices

The rise in portal pressure is associated with the development of collateral circulation, which allows the portal blood to be diverted into the systemic circulation. These spontaneous shunts occur (a) at the cardia through the intrinsic and extrinsic gastro-oesophageal veins; (b) in the anal canal where the superior haemorrhoidal vein belonging to the portal system anastomoses with the middle and inferior haemorrhoidal veins which belong to the caval system; (c) in the falciform ligament of the liver through the para-umbilical veins, which are the remains of the umbilical circulation of the fetus; (d) in the abdominal wall and the retroperitoneal tissues, from the liver to the diaphragm, veins in the lienorenal ligament, in the omentum and lumbar veins; and (e) blood diversion from the diaphragm, gastric, pancreatic, splenic, and adrenal veins, which may drain into the left renal vein.

Numerous lines of evidence suggest that varices develop and enlarge with time. Christensen et al[18] followed up a cohort of 532 patients with cirrhosis and showed that the cumulative incidence of patients with varices increased from 12% to 90% over 12 years. In a study involving 80 patients followed up for 16 months, Cales and Pascal[19] showed that 20% of patients who did not have varices developed new varices and 42% of patients with small varices showed definite enlargement. Czaja et al[20] also showed that the prevalence of varices increased from 8% to 13% over 5 years in a cohort of patients with chronic active hepatitis even though they were treated with prednisolone. Merli et al,[21] in a study of 213 patients with cirrhosis with no or small varices, demonstrated that the annual progression of varices was 12%. A recent database analysis by D'Amico et al[22]

using a competing risk model showed that the cumulative incidence of varices at 10 and 20 years was 44% and 53%, respectively, suggesting an overestimation in previous studies not using a competing risk model.

The main factors that appear to determine the development of varices are continued hepatic injury, the degree of portosystemic shunting, endoscopic appearances and portal pressure. Evidence for the role of hepatic injury is derived from studies in which varices were shown to regress with time. Baker et al[23] followed up a cohort of 115 patients with oesophageal varices and showed that varices had disappeared in nine patients, regressed in seven and remained unchanged in six. They concluded that the disappearance and regression of varices might be related to abstinence from alcohol. This observation was confirmed in a study by Dagradi[24] who followed up a cohort of patients with alcoholic cirrhosis over 3 years and showed a reduction in variceal size in 12 of the 15 patients with alcoholic cirrhosis who stopped drinking and an enlargement in variceal size in 17 patients who continued to drink. On the other hand, Cales and Pascal[19] showed that regression of varices occurred in 16% of patients with alcoholic cirrhosis who continued to imbibe alcohol. This might be related to the development of large portosystemic collaterals, which decompress the portal system and reduce the risk of the development of large oesophageal varices. The degree of portosystemic shunting can be quantified by measuring the diameter of portal veins and collaterals, and can be significant in those with gastrorenal or splenorenal shunting.[25 26] Others have shown that the presence of alcoholic cirrhosis, Child's B or C cirrhosis and red whale signs on index endoscopy predicted progression of varices.[21] Groszmann et al[27] in a placebo-controlled randomised trial of timolol in 213 cirrhotic patients without varices showed that a baseline hepatic venous pressure gradient (HVPG) of >10 mm Hg or a ≥10% increase in HVPG during follow-up were both predictive of the development of varices.

Diagnosis of gastro-oesophageal varices
Until recently, endoscopy has been used exclusively to diagnose varices. Non-invasive methods of screening for varices include capsule endoscopy, transient elastography and use of laboratory and radiological findings.

Endoscopy
There is universal acceptance that endoscopy is the 'gold standard' for diagnosing gastro-oesophageal varices. The main limitations are intraobserver variability in the diagnosis of small or grade I oesophageal varices (figure 1A–C). Recently, unsedated nasal gastroscopy has been found to have similar accuracy to conventional endoscopy and has the advantage of tolerability and potential cost saving since it can be performed in the clinic setting in some institutions.[28 29] However, there are no controlled studies and banding of varices is not possible.
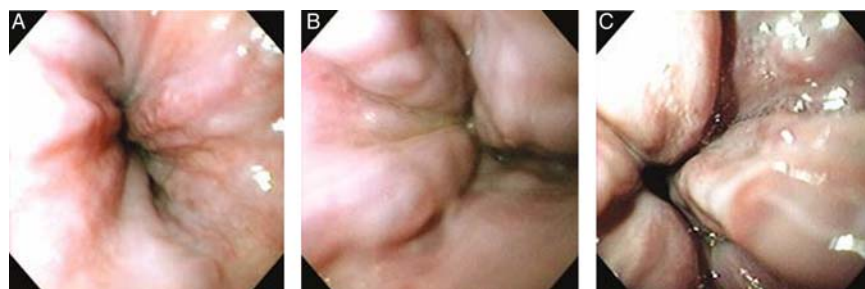
Capsule endoscopy
Capsule endoscopy uses a 26 mm pill-shaped device which transmits video footage which is stored and later analysed. Patients are not sedated, but patient cooperation is essential. In a large study by de Franchis et al,[30] capsule endoscopy was compared with standard gastroscopy. The primary end point of 90% or greater concordance was not achieved. Lapalus et al,[31] in a prospective study of 120 patients, demonstrated similar results with capsule endoscopy. Therefore, capsule endoscopy cannot be considered an alternative to standard endoscopy, although may have a role in patient who refuse gastroscopy.

Transient elastography
Transient elastography ((FibroScan, Echosens, Paris, France) uses the principles of ultrasound to derive tissue stiffness by measuring the speed of propagation of a low-frequency wave, which then correlates with liver fibrosis. Vizzutti et al[32] in a study of 61 patients with hepatitis C showed a sensitivity for prediction of oesophageal varices of 90% using a threshold 17.6 kPa. However, specificity was poor at 43%. A study of 298 patients found the optimal cut-off point for the prediction of oesophageal varices was 21.5 kPa (sensitivity 76% and specificity 78%).[33] In one uncontrolled study the use of transient elastography was found to be as effective as HVPG at predicting portal hypertension-related complications.[34] Therefore, the role of transient elastography in predicting varices is controversial due to the lack of consistent results and controlled studies. This modality may be more useful for predicting decompensation in patients with cirrhosis.

Radiological and serum parameters.
A prospective study of 311 patients with chronic hepatitis C showed that a platelet-to-spleen size ratio with a threshold of 909 had positive and negative predictive values of 100% and 94%, respectively.[35] These good results have not been reproduced by others as demonstrated in a meta-analysis.[36]

Risk factors for first variceal bleeding
The factors that predispose to, and precipitate, variceal haemorrhage are still not clear. The suggestion that oesophagitis may precipitate variceal haemorrhage has been discarded.[37] Presently, the most important factors that have been held responsible include (i) pressure within the varix, (ii) variceal size, (iii) tension on the variceal wall and (iv) severity of the liver disease.

Portal pressure
In most cases, portal pressure reflects intravariceal pressure[38] and a HVPG >10 mm Hg is necessary for the development of oesophageal varices.[27] There is no linear relationship between the severity of portal hypertension and the risk of variceal haemorrhage, although HVPG >12 mm Hg is an accepted

Figure 1 (A) Grade I oesophageal varices. These collapse to inflation of the oesophagus with air. (B) Grade II oesophageal varices. These are varices between grades 1 and 3. (C) Grade III oesophageal varices. These are large enough to occlude the lumen.

threshold for variceal bleeding.[39][40] However, the HVPG tends to be higher in bleeders as well as in patients with larger varices. In a prospective study comparing propranolol with placebo for the prevention of first variceal haemorrhage, Groszmann et al[41] showed that bleeding from varices did not occur if the portal pressure gradient (PPG) could be reduced to <12 mm Hg. Others have shown that a 20% reduction in portal pressure protects against further bleeding.[42] These haemodynamic goals have been accepted as the aim of pharmacological treatment of portal hypertension. It is important to appreciate that gastric varices can bleed at pressures <12 mm Hg, and the influence of wall tension of the varix plays a greater role in the risk of bleeding.[43] A greater pressure reduction may be necessary to protect against bleeding. This is further discussed in the section 'Gastric varices'. At present, measurement of portal pressure in guiding pharmacological treatments is limited to clinical trials in the UK.

Variceal size
Variceal size is best assessed endoscopically (figure 1A–C). Published results are variable owing to the lack of a definition distinguishing between large and small varices. Small (grade I) varices tend to be narrow and flatten easily with air, whereas larger (grade 2 and 3) varices are usually broader and flatten with difficulty, if at all. Numerous studies[40][44] have shown that the risk of variceal haemorrhage increases with the size of varices.[45]

Variceal wall and tension
Polio and Groszmann[46] using an in vitro model showed that rupture of varices was related to the tension on the variceal wall. The tension depends on the radius of the varix. In this model, increasing the size of the varix and decreasing the thickness of the variceal wall caused variceal rupture. Recently, endoscopic ultrasound and manometry have been used to estimate wall tension of varices.[47]

Endoscopic features such as 'red spots' and 'whale' markings were first described by Dagradi.[24] They have been described as being important in the prediction of variceal haemorrhage. These features represent changes in variceal wall structure and tension associated with the development of microtelangiectasias and reduced wall thickness. In a retrospective study by the Japanese Research Society for Portal Hypertension, Beppu et al[48] showed that 80% of patients who had blue varices or cherry red spots bled from varices, suggesting that this was an important predictor of variceal haemorrhage in cirrhosis.

Severity of liver disease and bleeding indices
Two independent groups prospectively assessed factors predicting first variceal haemorrhage in cirrhosis (table 2). The North Italian Endoscopic Club (NIEC)[49] reported their findings in 1988, followed in 1990 by data from the Japanese.[50] Both these studies showed that the risk of bleeding was based on three factors: severity of liver disease as measured by Child class, variceal size and red wale markings. The NIEC study showed a wide range for the risk of bleeding of 6–76%, depending on the presence or absence of the different factors. Using the same variables the NIEC index was simplified by de Franchis et al[51] and shown to correlate with the original index. Further studies showed that the HVPG and intravariceal pressure were also independent predictors of first variceal haemorrhage when analysed in conjunction with the NIEC index.[52][53]

In summary, the most important factors that determine the risk of variceal haemorrhage are the severity of liver disease, size of varices, and presence of red signs. Measurement of HVPG is a useful guide for selection of patients for treatment and their response to

Table 2 Scoring systems for quantifying the severity of cirrhosis
Severity of liver disease can be described using the Child–Pugh score or MELD score.
The Child–Pugh score is the sum of severity scores for Child class, variceal size and red wale markings the variables shown below.

Category	1	2	3
Encephalopathy	0	I/II	III/IV
Ascites	Absent	Mild-moderate	Severe
Bilirubin (μmol/L)	<34	34–51	>51
Albumin (g/L)	>35	28–35	<28
INR	<1.3	1.3–1.5	>1.5

Child–Pugh class A represents a score of ≤6, class B a score of 7–9, and class C, ≥10.
The MELD score is a formula that includes three laboratory-based variables reflecting the severity of liver disease. It was originally used to predict the short-term mortality after placement of a transjugular intrahepatic portosystemic stent-shunt for variceal bleeding. Subsequently, it has been used in selecting candidates for liver transplantation.
MELD score: please use the online calculator https://www.esot.org/Elita/meldCalculator.aspx.
INR, international normalised ratio.

treatment, although the predictive value does not appear to improve on the NIEC index and presence of red whale marking.[54]

Risk and mortality of first variceal bleed
Data describing the overall risk of bleeding from varices must be viewed with caution and have some pitfalls in interpretation. The natural history of patients who have varices that are diagnosed as part of their baseline investiations is different from that of patients who have complications of liver disease such as ascites and encephalopathy. Most studies do not comment on either the severity of liver disease or whether patients with alcoholic cirrhosis are continuing to drink. Both these factors have a significant effect on the risk of variceal haemorrhage.

Most studies report bleeding from varices in about 20–50% of patients with cirrhosis during the period of follow-up. Baker et al[23] reported variceal bleeding in 33 of 115 patients that they followed up for a mean of 3.3 years, with a mortality of 48% from the first variceal haemorrhage. These data were confirmed by Christensen et al.[18] About 70% of the episodes of bleeding occur within 2 years of diagnosis. Recent studies demonstrate a dramatic reduction in mortality following variceal bleeding of 20% 6-week mortality[55] and 15% in-hospital mortality,[5] with contributions from improved endoscopic, pharmacological and radiological therapies, notably TIPSS. Intensive care treatment has also improved, with outcomes being particularly good for those requiring minimal organ support.

Analysis of the non-active treatment arms in the primary prophylaxis trials comparing propranolol with placebo show results similar to those of the primary prophylaxis shunt trials, with most episodes of bleeding occurring within the first 2 years of follow-up. In these studies the rate of first variceal haemorrhage ranged from 22% to 61%.[56–60] This large difference in the rate of first bleed relates almost certainly to the number of patients with severe liver disease included in the study (Pascal, Child C—46%, bleeding—61%; Italian Multicenter Project for Propranolol in Prevention of Bleeding (IMPP), Child C—6%, bleeding—32%; Conn, Child C—6%, bleeding—22%). Mortality varied from 24% to 49% over 2 years (Pascal, mortality—49%; IMPP, mortality—24%; Conn, mortality—24%).

Primary prophylaxis
Since 30–50% of patients with portal hypertension will bleed from varices and about 20% will die from the effects of the first

bleed, it seems rational to develop prophylactic regimens to prevent the development of, and bleeding from, these varices. However, most of the published trials do not have sufficient power to identify favourable treatment effects. Based on the expected bleeding and death rates in the control group, the minimum number of patients needed to detect a 50% reduction in bleeding would be 270, and 850 patients in each arm to detect the same reduction in mortality. A proposed algorithm for surveillance and prophylaxis of varices is shown in figure 2. At this time there is insufficient evidence to support treating patients without varices or 'pre-primary prophylaxis'. A large randomised placebo-controlled trial of timolol in patients without varices and portal hypertension defined as HVPG >6 mm Hg did not show any effect on the development of varices or variceal bleeding.[27] The role of drug treatment in preventing bleeding in patients with small varices is unclear. Three randomised placebo-controlled trials have studied this. Cales et al[61] showed that propranolol in patients with small, or no, varices resulted in greater development of varices. However, patients without varices were included and there was significant loss of patients to follow-up. The second trial showed that nadolol reduced variceal bleeding without survival benefit and increased adverse events.[62] Sarin et al[63] did not show any effect with propranolol, despite a significant effect on portal pressure.

Surgery
Portacaval shunts
Four trials of portacaval shunts have been published, which randomised a total of 302 patients[64–67] either to prophylactic shunt surgery or to non-active treatment. A meta-analysis of these studies showed a significant benefit in the reduction of variceal bleeding (OR=0.31, 95% CI 0.17 to 0.56) but also a significantly greater risk of hepatic encephalopathy (OR=2, 95% CI 1.2 to 3.1) and mortality (OR=1.6, 95% CI 1.02 to 2.57) in patients treated with shunt surgery.[68] At this time, there is no evidence for the use of TIPSS for primary prophylaxis.[1]

Devascularisation procedures
Inokuchi[50] showed that there was a significant reduction in variceal bleeding and in mortality in patients treated with a variety of devascularisation procedures. There are, however, numerous problems with the interpretation of this study because of the use of different procedures in each of the 22 centres. These results require confirmation.

Pharmacological treatment
Non-cardioselective β blockers
The mainstay of the pharmacological approach to the primary prophylaxis of variceal haemorrhage has been NSBB. Propranolol which has been shown to reduce the PPG, reduce azygos blood flow, and also variceal pressure. It achieves this by causing splanchnic vasoconstriction and reducing cardiac output. There is no clear dose-related reduction in HVPG or correlation of HPVG reduction with reduction in heart rate.[69] Observational studies have shown that a 10–12% reduction in HVPG after acute administration of propranolol was associated with reduced bleeding and hepatic decompensation.[54 70] However, HVPG monitoring is not routinely available in most centres outside of larger institutions. A meta-analysis of nine placebo-controlled randomised trials (964 patients) showed that the pooled risk difference for bleeding was −11% (95% CI −21% to −1%), and for death was −9% (95% CI −18% to −1%) in favour of propranolol.[71]

Nadolol exerts similar effects on portal haemodynamics, although the effect on blood pressure may not be as pronounced. Two placebo-controlled trials[58 59] have shown reduced bleeding, although in one study this was only seen on per protocol analysis.[59] There was no effect on overall survival.

Carvedilol is a NSBB like propranolol, and a vasodilator due to α1 receptor blockade. The latter reduces portocollateral resistance, and by actions on hepatic stellate cells leads to a reduction in intrahepatic resistance. Haemodynamic studies demonstrate a greater reduction in portal pressure with
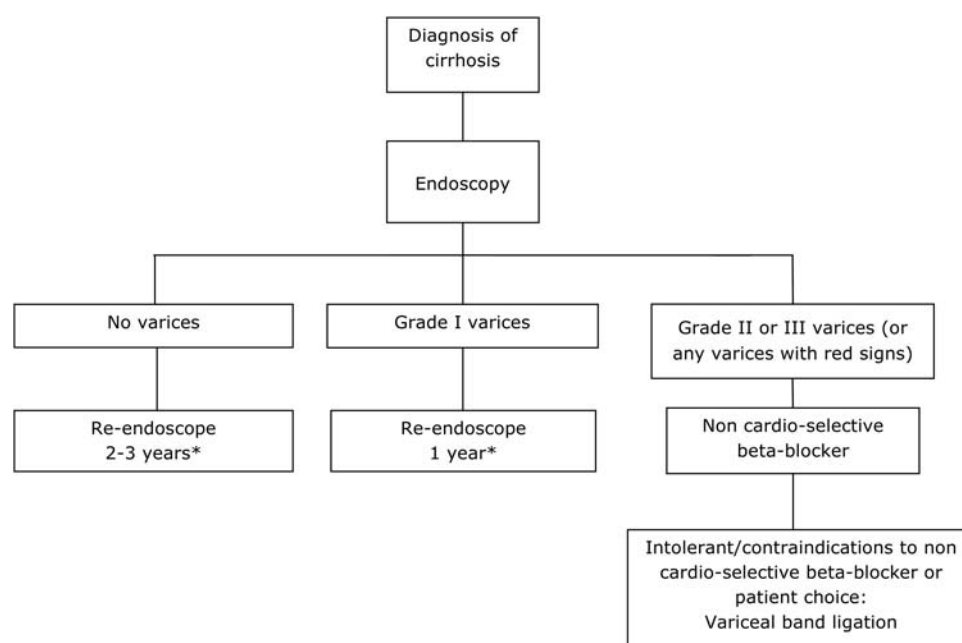
Figure 2 Algorithm for surveillance of varices and primary prophylaxis in cirrhosis.
*− If there is clear evidence of disease progression this interval can be modified by clinician. Endoscopy should also be offered at time of decompensation.

carvedilol than with propranolol, although blood pressure is reduced.[72 73] The optimum dose is 6.25–12.5 mg/day.[74] Higher doses are not more effective and are associated with more adverse events—in particular, hypotension. Carvedilol at a dose of 12.5 mg/day at current UK prices is considerably cheaper than propranolol 40 mg twice a day and nadolol 80 mg/day (monthly cost, £1.20, £5.62 and £5, respectively). Two RCTs of carvedilol versus variceal band ligation (VBL) in primary prophylaxis have been published.[75 76] The first study[75] showed significantly reduced bleeding in the carvedilol arm (10% vs 23%, relative hazard 0.41; 95% CI 0.19 to 0.96), with no effect on survival. The second trial by Shah et al[76] did not show any differences in bleeding or mortality. Compliance with VBL was better in the latter trial, and unlike the first trial, there were significantly more patients with viral hepatitis than alcoholic cirrhosis. A further study[74] assessed the effect of carvedilol in patients who were haemodynamic non-responders to propranolol, where haemodynamic response was defined as HVPG reduction to ≤ 12 mm Hg or by >20% of baseline after 4 weeks of treatment. Patients who were haemodynamic non-responders or intolerant to carvedilol were treated with VBL. Carvedilol resulted in significantly lower variceal bleeding compared with VBL, and haemodynamic responders to carvedilol or propranolol had significantly lower mortality than those treated with VBL. It is worth noting that the study was not randomised.

There have been recent suggestions based on low-level evidence that NSBB may result in a poorer outcome in patients with cirrhosis and refractory ascites.[77] The 'window hypothesis' for β blockers in cirrhosis has also recently been described, suggesting that NSBB are helpful in the compensated and early decompensated cirrhotic period, but may not be helpful in very early cirrhosis, such as in a patient with no varices, and may be harmful in patients with end-stage cirrhosis with refractory ascites.[78] However, recent large observational studies question the last hypothesis, with improved survival seen in patients with refractory ascites treated with NSBB,[79] unless patients have an episode of spontaneous bacterial peritonitis.[80] Therefore, until there are further prospective controlled studies, NSBB should be continued in patients with refractory ascites. The clinician must carefully monitor haemodynamic parameters such as blood pressure, and discontinue NSBB in patients with hypotension and renal impairment as can occur after an episode of spontaneous bacterial peritonitis. Other potentially severe adverse events with NSBB include symptomatic bradycardia, asthma and cardiac failure. Less severe side effects such as fatigue, insomnia and sexual dysfunction may also result.

Isosorbide mononitrate
Interest in the use of vasodilators such as isosorbide mononitrate (ISMN) developed after the demonstration that it reduces portal pressure as effectively as propranolol,[81] but has subsequently waned. A trial comparing ISMN with propranolol showed no significant difference between these agents.[82] Another randomised trial of ISMN versus placebo did show any difference in the two arms.[83] Therefore, ISMN is not recommended as monotherapy in primary prophylaxis.

β Blocker and ISMN
The combination of nadolol and ISMN has been compared with nadolol in a RCT. The combination therapy reduced the frequency of bleeding significantly but no significant differences were detected in mortality.[84] However, Garcia-Pagan et al[85] in a double-blind RCT of propranolol plus ISMN versus propranolol plus placebo failed to show any differences between the two arms. Combination therapy is associated with more side effects.

Proton pump inhibitors
A placebo-controlled randomised trial reported reduced bleeding and mortality with rabeprazole after eradication of varices.[86] However, the study had a heterogeneous population with VBL performed for both primary and secondary prophylaxis and small numbers (n=43), limiting the validity of the conclusions. Furthermore, there was no arm comparing proton pump inhibitors with NSBB. The use of proton pump inhibitors in patients with cirrhosis and ascites was associated with increased risk of spontaneous bacterial peritonitis in a large retrospective study.[87] This was not confirmed in a larger prospective non-randomised study.[88] However, a recent prospective observational study has shown proton pump use to be associated with increased mortality in cirrhosis.[89] Proton pump inhibitors are also associated with increased risk of Clostridium difficile infection.[90] There remains continuing concern about proton pump inhibitors in patients with cirrhosis, therefore caution should be used.

Endoscopic therapy
Variceal band ligation
VBL has been compared with NSBB in 19 trials in a recent Cochrane meta-analysis of 1504 patients.[91] Despite reduced bleeding (RR=0.67, 95% CI 0.46 to 0.98) with VBL, there was no difference in overall mortality and bleeding-related mortality. The difference in bleeding was not seen when only trials with low selection or attrition bias were included. Banding can have serious complications. The risk of fatal banding-induced bleeding was highlighted in a meta-analysis showing reduced fatal adverse events with NSBB (OR=0.14, 95% 0.02 to 0.99).[92] The optimal timing of banding intervals is discussed in the section 'Secondary prophylaxis of variceal haemorrhage'. A randomised trial of 96 patients who underwent endoscopic surveillance at 6 or 3 months after eradication of varices with VBL did not demonstrate a difference in bleeding on mortality.[93] However, the trial had a heterogeneous study group of patients who underwent VBL both for primary (65%) and secondary prevention (35%).

Sclerotherapy
Nineteen trials have compared endoscopic variceal sclerotherapy with no treatment.[68] Owing to the marked heterogeneity between these studies a meta-analysis is clinically inappropriate.[68] Sclerotherapy does not offer any benefit in combination with NSBB or VBL compared with VBL or NSBB alone, and increases iatrogenic complications such as strictures.[94–96] At this time sclerotherapy cannot be recommended for prophylaxis of variceal haemorrhage in patients with cirrhosis.

Recommendations: primary prophylaxis of variceal haemorrhage in cirrhosis (figure 2)
1. What is the best method for primary prophylaxis?
   1.1. We recommend NSBB or variceal band ligation (VBL). We suggest pharmacological treatment with propranolol as first line. VBL is offered if there are contraindications to NSBB. The choice of VBL or NSBB should also take into account patient choice (level 1a, grade A).
   1.2. We suggest carvedilol or nadolol as alternatives to propranolol (level 1b, grade A).
   1.3. Dose:
      1.3.1. Propranolol: 40 mg twice daily. Dose titrated to maximum tolerated or once heart rate (HR) of

50–55 bpm is reached to a maximum dose of 320 mg (level 1a, grade A).

1.3.2. Nadolol: 40 mg daily dose. Dose titrated to maximum tolerated or once HR of 50–55 bpm is reached a maximum dose of 240 mg (level 1a, grade A).

1.3.3. Carvedilol: 6.25 mg once daily to increase to maintenance of 12.5 mg after a week if tolerated or once HR of <50–55 bpm is reached (level 1a, grade A).

1.3.4. It is suggested that NSBB are discontinued at the time of spontaneous bacterial peritonitis, renal impairment and hypotension (level 2b, grade B).

1.4. In cases of contraindications or intolerance to NSBB, we recommend variceal band ligation (level 1a, grade A).

2. Who should have surveillance for variceal bleeding?

2.1. We recommend all patients with cirrhosis should be endoscoped at the time of diagnosis (level 1a, grade A). There is no indication to repeat endoscopy in patients receiving NSBB.

3. How often should cirrhotic patients be endoscoped?

3.1. If at the time of first endoscopy no varices are seen, we suggest that patients with cirrhosis should be endoscoped at 2–3-year intervals (level 2a, grade B).

3.2. If grade I varices are diagnosed, we suggest that patients should be endoscoped at yearly intervals (level 2a, grade B).

3.3. If there is clear evidence of disease progression we suggest that the intervals can be modified by a clinician. Endoscopy should also be offered at time of decompensation (level 2a, grade B).

4. Which patients with cirrhosis should have primary prophylaxis?

4.1. If grade I varices and red signs or grade 2–3 varices are diagnosed, we recommend that patients have primary prophylaxis irrespective of the severity of the liver disease (level 1a, grade A).

5. Treatments not recommended:

5.1. Proton pump inhibitors are not recommended unless otherwise required for peptic ulcer disease (level 1b, grade B).

5.2. Isosorbide mononitrate monotherapy is not recommended as primary prophylaxis (level 1b, grade A). There is insufficient evidence to recommend isosorbide mononitrate in combination with NSBB (level 1b, grade A).

5.3. Shunt surgery or TIPSS is not recommended as primary prophylaxis (level 1a, grade A).

5.4. Sclerotherapy is not recommended as primary prophylaxis (level 1a, grade A).

6. Areas requiring further study:

6.1. Role of NSBB in patients without varices, with focus on carvedilol.

6.2. Role of NSBB in patients with small varices, with focus on carvedilol.

6.3. Comparison of carvedilol versus propranolol in primary prophylaxis.

6.4. Identification of, and trials assessing, new drugs for primary prophylaxis such as statins.

7. Quality indicator:

7.1. Percentage of patients at diagnosis of cirrhosis who have had an endoscopy to screen for varices (level 1a, grade A).
Numerator; patients diagnosed with cirrhosis who have had an endoscopy either before or after diagnosis within 6 months.
Denominator; patients newly diagnosed with cirrhosis.

7.2. Percentage of patients receiving primary prophylaxis among those newly diagnosed with grade I varices and red signs or grade 2–3 varices.
Numerator; patients who have grade 1 varices with red signs or grade 2–3 varices receiving primary prophylaxis.
Denominator; patients diagnosed with cirrhosis who have grade I varices with red signs or grade 2–3 varices.

MANAGEMENT OF ACTIVE VARICEAL HAEMORRHAGE

The average 6-week mortality of the first episode of variceal bleeding in most studies is reported to be up to 20%. There has been considerable improvement in survival since the early 1980s when the in-hospital mortality was 40–50%,[97] compared with 15% from a recent UK audit.[5] Such is the improvement in outcomes, that a patient with Child's A cirrhosis is very unlikely to succumb to an index variceal bleed. Studies have shown the Child–Pugh score, MELD score, and HVPG to be strong predictors of outcomes.[98–103] The MELD score has been shown to outperform Child's score in a recent study, with a score >19 associated with 20% 6 week mortality.[103] Furthermore, the MELD score has been shown to perform as well as the traditional intensive care unit scores in predicting mortality in patients admitted to intensive care in the UK.[104] MELD >18, active bleeding, transfusing >4 units of packed red blood cells have been shown to be predictors of mortality and early rebleeding.[99 101 102] HVPG has also been shown to predict outcome when measured at 2 weeks after a bleed,[44] and a value of ≥20 mm Hg when measured acutely within 48 h has been shown to provide significant prognostic information.[100] However, this technique is not used routinely in the management of patients around the world, and substitution of clinical data in the latter study was shown to provide the same clinical predictive value.[100] These scoring systems are not purely academic; they allow the referring clinician to predict those patients with a high chance of rebleeding to be transferred to a specialist centre offering, for instance, TIPSS before the patient rebleeds.

Nonetheless, probably the most important step in the management of acute variceal haemorrhage is the initial resuscitation assessed according to standard 'ABC' practice, together with protection of the airway to prevent aspiration. Although early endoscopy allows for accurate diagnosis of the bleeding site and decisions about management (figure 3), therapeutic intervention in acute variceal bleeding can be initiated, safely in most cases, before diagnostic endoscopy. As similar efficacy is demonstrated with pharmacological treatment as with sclerotherapy, the former should be first-line therapy.[99] β Blockade should not be started in the acute setting, and those already taking β blockers as prophylaxis should probably stop taking them for 48–72 h in order that the patient's physiological response to blood loss can be allowed to manifest.
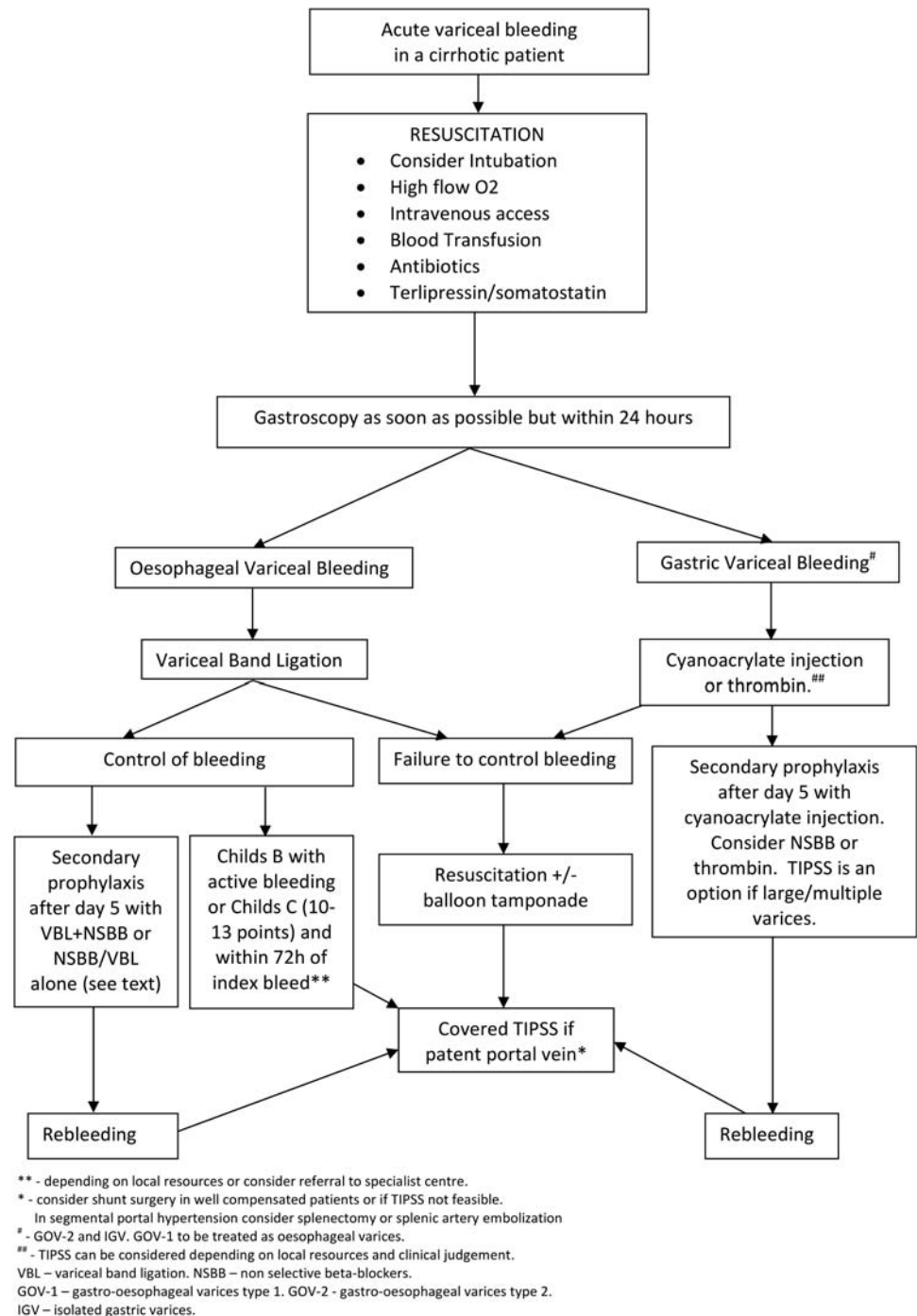
General considerations
Patient evaluation

The majority of patients with a variceal bleed will be sufficiently stable to enable a full history and examination to take place. History of alcohol excess and or intravenous drug use should be sought and may become particularly relevant if the patient has withdrawal symptoms after admission. Comorbidity is important when estimating risk and deciding on use of vasopressors. The

Figure 3 Algorithm for the management of acute variceal bleeding. TIPSS, transjugular intrahepatic portosystemic stent shunt.

Acute variceal bleeding in a cirrhotic patient

RESUSCITATION
- Consider Intubation
- High flow O2
- Intravenous access
- Blood Transfusion
- Antibiotics
- Terlipressin/somatostatin

Gastroscopy as soon as possible but within 24 hours

Oesophageal Variceal Bleeding

Gastric Variceal Bleeding#

Variceal Band Ligation

Cyanoacrylate injection or thrombin.##

Control of bleeding

Failure to control bleeding

Secondary prophylaxis after day 5 with cyanoacrylate injection. Consider NSBB or thrombin. TIPSS is an option if large/multiple varices.

Secondary prophylaxis after day 5 with VBL+NSBB or NSBB/VBL alone (see text)

Childs B with active bleeding or Childs C (10-13 points) and within 72h of index bleed**

Resuscitation +/- balloon tamponade

Covered TIPSS if patent portal vein*

Rebleeding

Rebleeding

** - depending on local resources or consider referral to specialist centre.
* - consider shunt surgery in well compensated patients or if TIPSS not feasible.
In segmental portal hypertension consider splenectomy or splenic artery embolization
- GOV-2 and IGV. GOV-1 to be treated as oesophageal varices.
- TIPSS can be considered depending on local resources and clinical judgement.
VBL – variceal band ligation. NSBB – non selective beta-blockers.
GOV-1 – gastro-oesophageal varices type 1. GOV-2 - gastro-oesophageal varices type 2.
IGV – isolated gastric varices.

following risk factors doubled mortality after an acute variceal bleed in one US study: older age, comorbidities, male gender and not undergoing a gastroscopy within 24 h.[105]

A full examination is helpful for the important negatives as much as the positives. Baseline observations should include the temperature, as infection is a serious complication with significant mortality. Confusion may be present because of encephalopathy, intoxication with alcohol or drugs or withdrawal from alcohol or drugs. The patient should be on continuous BP and pulse monitor and their haemodynamic status recorded. An oxygen saturation monitor is helpful. Stigmata of chronic liver disease and concurrent jaundice provide insight into the current status of a patient's liver, and also give warning of potential further decompensation if significant bleeding persists (see scoring systems above). Pneumonia must be actively

excluded. Evidence of ascites requires a diagnostic tap to search for infection.

Investigations including full blood count, coagulation profile, liver and renal function and blood group and save and cross-match. Blood and urine should also be cultured. An ultrasound scan later in the admission is helpful to identify subclinical ascites, flow in portal vein and any obvious emergence of an hepatocellular carcinoma (HCC).

Location of patient
A decision must be made as to where the patient is best managed. Variceal bleeding is unpredictable, generally occurs in patients with significant liver disease and is associated with significant mortality. Hence, a high-dependency unit is usually the most appropriate initial location, although a properly staffed 'gastrointestinal

bleeding bed' may be appropriate. If a patient is vomiting blood, or there is a perceived risk of a haemodynamically unstable patient having blood in the stomach, then the patient must be intubated before endoscopy, and return to an intensive care or high-dependency unit will be necessary until extubation.

Volume resuscitation and blood products

Intravenous access (two 16–18G cannulae) should have been secured on admission with a reported GI bleed. Further intravenous access may be necessary. In patients with poor venous access, advanced liver disease, or renal failure associated with their liver disease, central venous access may be helpful with guiding fluid infusions. However, the drawbacks include the risk of the procedure and a potential source of infection. Therefore, there is no absolute requirement for a central line, and no evidence of unequivocal benefit. Intravenous fluid resuscitation should be initiated with plasma expanders aiming to maintain a systolic blood pressure of 100 mm Hg. Care with monitoring is paramount in this group of patients.

Overtransfusion has been shown to have a deleterious effect on outcome. In a recent single-centre RCT, a restrictive transfusion policy of maintaining haemoglobin between 70 and 80 g/L improved the control of variceal bleeding (11% vs 22%, p=0.05), and lowered HVPG compared with a liberal transfusion policy without effect on 45-day survival.[106] However, it should be noted that these results were from a single Spanish centre, which was a tertiary unit for variceal bleeding, where all patients underwent endoscopy within 6 h. Nonetheless, a restrictive transfusion policy has been recommended for some time[1] and there is now good evidence to support not transfusing a stable patient with a haemoglobin of ≥80 g/L. However, under-resuscitation should also be avoided and while goal-oriented fluid replacement has generally not been useful in an intensive therapy unit setting, a venous saturation >70% remains an easily measurable target with some evidence to support it.[107]

Interpretation and management of clotting profile is challenging in liver disease, where there is usually a balanced deficiency of both procoagulant and anticoagulant factors.[108] The NICE guidelines recommend activation of a hospital's massive transfusion policy when there is major haemorrhage, and platelet support when the value is <50, and clotting factor support when the international normalised ratio (INR) is >1.5 times normal.[2] There is no evidence for the use of 'prophylactic' clotting or platelet support to reduce the risk of rebleeding. There is insufficient evidence to support the routine use of transexamic acid, or recombinant factor VIIa.[109]

Pharmacological treatment

The two major classes of drugs that have been used in the control of acute variceal bleeding are vasopressin or its analogues (either alone or in combination with nitroglycerine) and somatostatin or its analogues. Terlipressin is the only agent that has been shown to reduce mortality in placebo-controlled trials. However, in trials comparing terlipressin, somatostatin and octreotide, no difference in efficacy was identified in a systematic review[110] and in a recent large RCT.[111] Prophylactic antibiotics can result in a similar survival benefit following acute variceal bleeding.

Vasopressin

Vasopressin reduces portal blood flow, portal systemic collateral blood flow and variceal pressure. It does, however, have significant systemic side effects such as an increase in peripheral resistance, and reduction in cardiac output, heart rate and coronary blood flow. In comparison with no active treatment, the pooled results of four randomised trials showed that it reduced failure to control variceal bleeding (OR=0.22, 95% CI 0.12 to 0.43), although survival was unaffected.[68] Meta-analysis of five trials comparing sclerotherapy with vasopressin has shown a significant effect on reduction in failure to control bleeding (OR=0.51, 95% CI 0.27 to 0.97), with no effect on survival.[68]

Vasopressin with nitroglycerine

The addition of nitroglycerine enhances the effect of vasopressin on portal pressure and reduces cardiovascular side effects.[112] Meta-analysis of three randomised trials comparing vasopressin alone with vasopressin and nitroglycerine showed that the combination was associated with a significant reduction in failure to control bleeding (OR=0.39, 95% CI 0.22 to 0.72), although no survival benefit was shown.[68]

Terlipressin

Terlipressin is a synthetic analogue of vasopressin, which has an immediate systemic vasoconstrictor action followed by portal haemodynamic effects due to slow conversion to vasopressin. In a Cochrane meta-analysis of seven placebo-controlled trials, terlipressin was shown to reduce failure to control bleeding (RR=0.66, 95% CI 0.55 to 0.93) and also to improve survival (RR=0.66, 95% CI 0.49 to 0.88).[113] In the same meta-analysis, there was no difference between terlipressin versus vasopressin, balloon tamponade or endoscopic therapy in failure to control bleeding or survival.[113] The role of terlipressin in combination with VBL is explored in the section 'Endoscopic therapy in combination with pharmacological therapy'.

The recommended dose of terlipressin is 2 mg IV every 4 h, although many units reduce the dose to 6 hourly as it may cause peripheral vasoconstriction which manifests as painful hands and feet. While 5 days of IV treatment has been advocated in the Baveno V guidelines,[1] this prolonged treatment has not been shown to have a survival benefit, and for pragmatic reasons many units will stop treatment shortly after satisfactory haemostasis. In a randomised trial terlipressin given for 24 h after satisfactory haemostasis with VBL after oesophageal variceal bleeding was as effective as 72 h of treatment.[114]

In patients intolerant of terlipressin or in countries where terlipressin is not available, alternatives should be considered.

Somatostatin and octreotide

Somatostatin causes selective splanchnic vasoconstriction and reduces portal pressure and portal blood flow.[115] Octreotide is a somatostatin analogue. The mechanism of action of these two agents is not clear. Inhibition of glucagon increases vasodilatation rather than a direct vasoconstrictive effect and post-prandial gut hyperaemia is also reduced. The actions of octreotide on hepatic and systemic hemodynamics are transient, making continuous infusion necessary. Octreotide is given as a 50 µg bolus followed by an infusion of 25–50 µg/h. Somatostatin is given as a 250 mg intravenous bolus followed by an infusion of 250 mg/h. Somatostatin and octreotide have been shown to be as effective as terlipressin in acute variceal bleeding in a meta-analysis.[110] Seo et al[111] in a large RCT of 780 patients comparing these three agents failed to show a difference in treatment success (range 83.8–86.2%), rebleeding (range 3.4–4.4%) and mortality (range 8–8.8%). A low systolic blood pressure at presentation, high serum creatinine level, active bleeding in the emergency endoscopy, gastric variceal bleeding and Child–Pugh grade C were independent factors predicting 5-day treatment failure.[111]

Antibiotics

Antibiotics that provide Gram-negative cover are one of the interventions which positively influence survival in variceal haemorrhage as shown in a Cochrane meta-analysis of 12 placebo-controlled trials (RR=0.79, 95% CI 0.63 to 0.98).[116] Antibiotics were also shown to reduce bacterial infections (RR=0.43, 95% CI 0.19 to 0.97) and early rebleeding (RR=0.53, 95% CI 0.38 to 0.74).[116] Therefore, short-term antibiotics should be considered standard practice in all cirrhotic patients who have a variceal bleed, irrespective of the presence of confirmed infection. Third-generation cephalosporins, such as ceftriaxone (1 g IV, daily), have been shown to be more effective at reducing Gram-negative sepsis than oral norfloxacin,[117] but choice of antibiotics must be dictated by local resistance patterns and availability.

Proton pump inhibitors

One RCT compared a short course of proton pump inhibitors with vasoconstrictor therapies after haemostasis in acute variceal bleeding.[118] Despite larger ulcers noted in the vasoconstrictor arm, there were no differences in bleeding or survival. Nearly 50% of patients had ascites, which might have implications in light of the reports of increased incidence of spontaneous bacterial peritonitis as mentioned earlier.

Endoscopic therapy

Endoscopy should take place within 24 h of admission and earlier if there is excessive bleeding, based on low-level evidence.[105] While many guidelines and reviews suggest that endoscopy should be carried out within 12 h the only study that examined the influence of timing on outcome failed to demonstrate any advantage of endoscopy before 12 h.[119] The optimal time is after sufficient resuscitation, and pharmacological treatment, with the endoscopy performed by a skilled endoscopy team, in a suitably equipped theatre environment and with airway protection. Airway protection is essential where risk of aspiration is high, and affords the endoscopist time for thorough evaluation, including complete clot aspiration and controlled application of treatment, including tamponade if required. The endoscopy team must comprise an experienced endoscopy nurse acquainted with the equipment necessary for endoscopy therapy of varices, and a skilled endoscopist, competent in using banding devices and deployment of balloon tamponade.

Variceal band ligation

This technique is a modification of that used for the elastic band ligation of internal haemorrhoids. Its use in humans was first described in 1988.[120] A meta-analysis of seven trials comparing VBL with sclerotherapy in acute bleeding showed that VBL reduced rebleeding from varices (OR=0.47, 95% CI 0.29 to 0.78), reduced mortality (OR=0.67, 95% CI 0.46 to 0.98) and resulted in fewer oesophageal strictures (OR=0.10, 95% CI 0.03 to 0.29).[121] The number of sessions required to obliterate varices was lower with VBL (2.2 fewer sessions (95% CI 0.9 to 3.5)).

Sclerotherapy

Sclerotherapy has been replaced by VBL and should no longer be offered as standard of care in acute variceal haemorrhage.

Other endoscopic measures

In an RCT, cyanoacrylate offered no benefit over VBL, with the additional risk of embolisation and trend towards increased rebleeding with cyanoacrylate.[122]

Haemostatic powder (TC-325; Hemospray; Cook Medical, USA) has been described in a small study of nine patients who received endoscopic spray treatment for acute variceal bleeding. The study reported no rebleeding within 24 h and no mortality at 15 days.[123]

Endoscopic therapy in combination with pharmacological therapy

The role of combining vasoactive drugs with endoscopic therapy (VBL or sclerotherapy) was reported in a meta-analysis of eight trials.[124] Combination therapy resulted in better initial control of bleeding (RR=1.12, 95% CI 1.02 to 1.23), and 5-day haemostasis (RR=1.28, 95% CI 1.18 to 1.39), without any difference in survival. Adverse events were similar in both groups. Two RCTs have compared VBL with sclerotherapy in combination with vasoactive agents in acute variceal bleeding.[125 126] Lo et al[125] used vasopressin and found that VBL resulted in better 72 h haemostasis (97% vs 76%, p=0.009), with fewer complications (5% vs 29%, p=0.007). Villanueva et al used somatostatin, and reported lower failure to control acute bleeding with VBL (4% vs 15%, p=0.02), with fewer serious complications (4% vs 13%, p=0.04). Overall survival was similar in both trials.[125 126]

Balloon tamponade

Balloon tamponade is highly effective and controls acute bleeding in up to 90% of patients although about 50% rebleed when the balloon is deflated.[127 128] It is, however, associated with serious complications such as oesophageal ulceration and aspiration pneumonia in up to 15–20% of patients. Despite this, it may be a life-saving treatment in cases of massive uncontrolled variceal haemorrhage pending other forms of treatment. An appropriately placed Sengstaken–Blakemore tube allows for resuscitation, safe transportation and either repeat endoscopy or radiological shunting in a patient with a stable cardiovascular system. The oesophageal balloon is rarely required, must never be used on its own and should be used only if there is continuing bleeding despite an adequately inflated gastric balloon correctly placed and with appropriate tension. Placement of the tube endoscopically or over a guide wire might reduce the risk of complications, especially oesophageal rupture.

Removable oesophageal stents

The SX-Ella Danis stent (ELLA-CS, Hradec Kralove, Czech Republic) is a removable covered metal mesh stent placed endoscopically in the lower oesophagus without radiological screening. It has no role in the management of gastric variceal bleeding. These stents can be left in situ for up to 2 weeks unlike the Sengstaken–Blakemore tube which should be removed after a maximum of 24–48 h.[129 130] No published controlled trials have compared this modality with balloon tamponade.

Transjugular intrahepatic portosystemic stent-shunt

Several uncontrolled studies have examined the role of salvage bare TIPSS in acute variceal bleeding. In a review of 15 studies, control of bleeding was achieved in 90–100%, with rebleeding in 6–16%.[131] Mortality varied between 75% (in hospital) and 15% (30 day). It is important to appreciate that sclerotherapy was used as first-line endoscopic therapy in most of these studies. Long-term follow-up of a study that compared TIPSS with H-graft portacaval shunts in patients for whom non-operative management had failed suggested that H-grafts were a useful method of reducing portal pressure and had a significantly lower failure rate (p=0.04), but had no significant

improvement in overall survival despite a benefit seen in Child's A and B disease.[132] A recent RCT compared emergency porto-caval surgery with bare TIPSS within 24 h of presenting with acute oesophageal variceal bleeding in unselected cirrhotic patients. Emergency portocaval surgery resulted in better outcomes for long-term bleeding control, encephalopathy and survival (p<0.001).[133] Before wider application of surgery for acute variceal bleeding, more data are needed in light of the recent adoption of covered stents.

There has also been a generalised established change in practice in using covered TIPSS stents (polytetrafluoroethylene (PTFE)) rather than a bare metal stent, with evidence to support this change. In randomised controlled studies, these stents were shown to have higher primary patency rates than bare stents, without significant differences in survival, and the potential for reduced incidence of hepatic encephalopathy.[134 135]

There is, however, growing evidence from two RCTs for the earlier use of TIPSS in selected patients stratified by HVPG, Child–Pugh class and active bleeding, and not just use as a salvage option.[6 136] Monescillo et al[136] randomised patients presenting with acute oesophageal variceal haemorrhage to bare TIPSS or standard of care if the HVPG was ≥20 mm Hg within 24 h of admission. Significantly reduced treatment failure, as defined by failure to control acute bleeding and/or early rebleeding (12% vs 50%), was seen and improved survival (62% vs 35%) in the patients randomised to undergo a TIPSS procedure. However, the standard of care was sclerotherapy and not combination endoscopic and pharmacological treatment. This limitation and the lack of availability of HVPG measurement in most centres meant this trial did not have a significant impact on clinical practice.

Garcia-Pagan et al[6] selected patients with active bleeding and Child's B cirrhosis or patients with Child's C cirrhosis (Child's score <14) for randomisation to early PTFE-covered TIPSS within 72 h or standard of care with VBL and pharmacological treatment. This has shown encouraging results with reduced risk of treatment failure (3% vs 50%), improved survival (86% vs 61% at 1 year), yet without increased risk of hepatic encephalopathy. The results were supported by an observational study from the same group, although a survival benefit was not seen.[137] Furthermore, a recent well-conducted observational study did not demonstrate such high survival rates with early TIPSS, with 11-year survival of 67%, which was similar to that of patients given endoscopic and pharmacological treatments only.[138] Therefore, larger multicentred RCTs need to be undertaken to further evaluate the role of early TIPSS. It is important to make the distinction between salvage TIPSS and early TIPSS to prevent rebleeding.

Liver transplantation

This is probably appropriate only for patients who bleed while awaiting liver transplantation, although studies comparing VBL or TIPSS placement with urgent liver transplantation in this situation need to be done. Liver transplantation is an exceedingly rare option for the vast majority of patients, both because it is not commonly available and because of shortages and delays in organ procurement. No controlled trials of liver transplantation in uncontrolled/active bleeding are available.

Recommendations for the control of variceal bleeding in cirrhosis are given below and in figure 3.

Recommendations: control of active variceal haemorrhage in cirrhosis (figure 3)

1. Suggestions for resuscitation and initial management

1.1. Units offering an emergency acute upper gastrointestinal bleeding service should have expertise in VBL, balloon tamponade and management of gastric variceal bleeding (level 5, grade D).

1.2. Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding (level 5, grade D).

1.3. Base decisions on blood transfusion on the full clinical picture, recognising that overtransfusion may be as damaging as undertransfusion. A restrictive transfusion policy aiming for a haemoglobin of 70–80 g/L is suggested in haemodynamically stable patients (level 1b, grade B).

1.4. Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable (level 5, grade D).

1.5. Offer platelet transfusion to patients who are actively bleeding and have a platelet count of $<50 \times 10^9$/L (level 5, grade D).

1.6. Offer fresh frozen plasma to patients who have either:
   ▸ a fibrinogen level of <1 g/L (level 5, grade D), or
   ▸ a prothrombin time (international normalised ratio) or activated partial thromboplastin time >1.5 times normal (level 5, grade D).

1.7. Offer prothrombin complex concentrate to patients who are taking warfarin and actively bleeding (level 5, grade D).

1.8. Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols (level 5, grade D).

1.9. There is insufficient evidence for the use of recombinant factor VIIa in acute variceal haemorrhage (level 1b, grade B).

2. Suggestions for timing of upper gastrointestinal endoscopy:

2.1. Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation (level 5, grade A).

2.2. Offer endoscopy within 24 h of admission to all other patients with upper gastrointestinal bleeding (level 2b, grade A).

2.3. Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances (level 5, grade D).

3. Control of bleeding:

3.1. Antibiotics are recommended for all patients with suspected or confirmed variceal bleeding (level 1a, grade A).

3.2. In all patients, vasoconstrictors such as terlipressin or somatostatin are recommended and should be started as soon variceal bleeding is suspected and continued until haemostasis is achieved or for up to 5 days. Octreotide (unlicensed) is suggested if terlipressin or somatostatin are unavailable (level 1a, grade A).

3.3. Variceal band ligation is recommended as the preferred endoscopic method (level 1a, grade A).

3.4. After satisfactory haemostasis with the methods above, and depending on local resources, early covered TIPSS (<72 h after index variceal bleed) can be considered in selected patients with Child's B cirrhosis and active bleeding or Child's C cirrhosis with Child's score <14 (level 1b, grade B).

3.5. Proton pump inhibitors are not recommended unless otherwise required for peptic ulcer disease (level 1b, grade B).

4. Failure to control active bleeding:

4.1. If bleeding is difficult to control, a Sengstaken–Blakemore tube should be inserted until further endoscopic treatment, TIPSS or surgery is performed depending on local resources and expertise (level 1b, grade B).

4.2. Specialist help should be sought at this time and transfer to a specialist centre should be considered. Units that do not offer a TIPSS service should identify a specialist centre which offers a 24 h emergency TIPSS service and have appropriate arrangements for safe transfer of patients in place (level 2a, grade B).

5. Areas requiring further study:

5.1. The efficacy of restrictive blood transfusion in variceal haemorrhage.

5.2. The role of blood products in variceal haemorrhage.

5.3. The utility of early TIPSS (<72 h) in acute variceal haemorrhage.

5.4. The role of removable oesophageal stents in acute variceal haemorrhage.

5.5. The role of haemostatic powders in acute variceal haemorrhage.

5.6. The role of proton pump inhibitors in variceal haemorrhage.

6. Quality indicators:

6.1. Antibiotic administration in acute variceal bleeding within 1 day either before or after the procedure (level 1a, grade A).
Numerator; patients with an acute variceal bleed who have received antibiotics within 1 day either before or after the procedure.
Denominator; patients with an acute variceal bleed.

6.2. Endoscopy performed within 24 h of presentation of an acute variceal bleed (level 2b, grade A).
Numerator; patients with an acute variceal bleed who have received endoscopy within 24 h of presentation.
Denominator; patients with an acute variceal bleed.

SECONDARY PROPHYLAXIS OF VARICEAL HAEMORRHAGE
β Blockers
A meta-analysis of 12 trials comparing propranolol or nadolol[139] with no active treatment showed a significant reduction in rebleeding but no significant reduction in mortality.[140] The greater reduction in portal pressure with carvedilol compared with propranolol has been described in the section 'Primary prophylaxis' of this guideline.

Nitrates
The addition of ISMN to NSBB has been shown to reduce variceal rebleeding compared with NSBB alone, although no survival benefit was seen.[141] In addition, adverse events leading to drug withdrawal were more common in the group receiving combined drug treatment. A meta-analysis of ISMN alone or with either NSBB or endoscopic therapy reported that there was no mortality benefit from combining nitrates and NSBB compared with NSBB alone.[142]

Side effects of ISMN include dizziness and headache. Owing to the side effects and relative lack of data, ISMN is not commonly used in clinical practice.

A recent RCT of 121 patients reported carvedilol to be similar to combined ISMN and NSBB therapy in the prevention of variceal rebleeding and mortality, although severe adverse events were less common with carvedilol.[143]

Simvastatin
A recent abstract of a multicentre RCT of 158 patients reported a survival benefit (91% vs 78%, p=0.03) from adding simvastatin to VBL and NSBB compared with placebo, VBL and NSBB, as treatment for the prevention of variceal rebleeding.[144] There was no difference in rebleeding and the survival benefit was restricted to Child A and B patients. Serious adverse events were similar in both groups. More data are required to investigate this interesting observation of a survival benefit from simvastatin in this situation, which may relate to its effects on hepatocellular function, fibrosis and portal pressure.

Proton pump inhibitors
A double-blind randomised placebo-controlled trial showed that pantoprazole reduced the size of ulcers in patients who underwent VBL. However, the total number of ulcers and other outcomes were similar in the two groups.[145]

Endoscopic therapy
VBL has been accepted as the preferred endoscopic treatment for the prevention of variceal rebleeding, with a lower rate of rebleeding, mortality and complications than sclerotherapy.[146 147] The time interval between VBL sessions to achieve eradication of varices is debateable. However, a recent RCT comparing monthly with biweekly VBL after initial haemostasis with VBL in 70 patients suggested that there were fewer post-VBL ulcers in the monthly group (11% vs 57%; p<0.001).[148] Variceal recurrence, rebleeding and mortality were similar in both groups.

Two meta-analyses showed there is no evidence that the addition of sclerotherapy to VBL improves clinically relevant outcomes, including variceal rebleeding and death, and the combination led to higher stricture rates.[149 150]

Endoscopic therapy versus drug therapy
VBL has been reported to be more effective than combined NSBB and ISMN drug therapy.[151] However, an 8-year follow-up study of this RCT found that although VBL was superior in reducing variceal rebleeding, survival rates were significantly higher in the group treated with combined drug treatment.[152] Other studies have found no superiority of VBL over combined drug therapy for prevention of variceal rebleeding or mortality.[153 154] A recent small multicentre RCT reported carvedilol to be similar to VBL in the prevention of variceal rebleeding, with a trend in favour of survival with carvedilol (73% vs 48%, p=0.110).[155]

Several meta-analyses have compared drug therapy with VBL in the prevention of variceal rebleeding. One meta-analysis of six RCTs showed no significant difference in variceal rebleeding rates when comparing VBL alone with combined NSBB and ISMN therapy. However, all-cause mortality was significantly higher in patients treated with the VBL (RR=1.25, 95% CI 1.01 to 1.55).[156] Three meta-analyses comparing drug therapy (NSBB alone or with ISMN) with endoscopic therapy alone reported no difference in variceal rebleeding or mortality.[157–159]

Endoscopic+drug therapy versus either alone
Numerous studies and several meta-analyses have compared combined endoscopic and drug therapy with monotherapy (endoscopic or drugs alone) in the prevention of variceal rebleeding. A meta-analysis of 23 trials assessing sclerotherapy or VBL combined with NSBB reported that combination therapy reduced rebleeding more than either endoscopic

therapy or NSBB alone (pooled RR=0.68, 95% CI 0.52 to 0.89), although no difference in mortality was detected.[160]

A meta-analysis of fewer studies suggested no significant difference in rebleeding between combined drug and VBL therapy and either alone.[157] A further meta-analysis reported reduced variceal rebleeding (RR=0.601, 95% CI 0.440 to 0.820) but similar mortality with combined drug and endoscopic therapy versus endoscopic therapy alone.[159] Another meta-analysis of 17 trials (14 using sclerotherapy and three using VBL) reported that combined endoscopic and NSBB therapy reduced rebleeding (OR=2.20, 95% CI 1.69 to 2.85) and overall mortality (OR=1.43, 95% CI 1.03 to 1.98) compared with endoscopic therapy alone.[161]

A further meta-analysis of 10 RCTs suggested that combination therapy reduces the risk of rebleeding from oesophageal varices compared with VBL (RR=0.68, 95% CI 0.45 to 0.93) or medical treatment (RR=0.60, 95% CI 0.43 to 0.84).[162] This meta-analysis included seven trials comparing combination therapy with VBL and three trials comparing combination therapy with drug treatment. Combined VBL and drug therapy gave a survival benefit when compared with VBL alone (RR=0.52, 95% CI 0.27 to 0.99), but not when compared with medical treatment alone.

Another recent meta-analysis assessed five studies comparing VBL alone with combination VBL and drug therapy, and four studies comparing drugs alone or combined with VBL.[163] This found that adding drugs to VBL reduced rebleeding (RR=0.44, 95% CI 0.28 to 0.69) with a trend towards reduced mortality, but adding VBL to drug treatment did not significantly affect either rebleeding or mortality.

The meta-analyses are not entirely consistent, although it would appear that combined VBL and drug treatment might improve survival, but is likely to increase adverse effects compared with VBL alone. There appears to be less clear benefit from combined VBL and drug treatment compared with drug treatment alone.

Transjugular intrahepatic portosystemic stent-shunt

Three meta-analyses comparing TIPSS with endoscopic treatment (sclerotherapy or VBL) have been published.[164–166] The results are similar, with the largest meta-analysis of 12 RCTs showing that (bare) TIPSS reduces variceal rebleeding (OR=0.32, 95% CI 0.24 to 0.43), but is associated with an increased risk of encephalopathy (OR=2.21, 95% CI 1.61 to 3.03).[166] No differences in survival were seen.[164–166] Despite the problem of shunt insufficiency and the cost of shunt surveillance, TIPSS has been shown to be more cost-effective than endoscopic therapy.[167]

A meta-analysis of six studies comparing TIPSS (both bare and covered) with or without variceal embolisation showed that adjuvant embolisation during TIPSS reduced rebleeding (OR=2.02, 95% CI 1.29 to 3.17) with similar shunt dysfunction, encephalopathy and mortality rates.[168] However, owing to heterogeneity of the study methodology, the authors recommended larger randomised studies using covered stents to confirm the findings. Generally, TIPSS placement using PTFE-covered stents[134] is recommended for patients for whom endoscopic and pharmacological treatment for the prevention of variceal rebleeding fails.[1]

The evidence for undertaking an 'early' TIPSS procedure[6] in patients shortly after a first variceal bleed has been discussed in the "Management of acute variceal bleeding" section of this guideline.

Surgery

A meta-analysis demonstrated that non-selective shunts reduced rebleeding compared with no active treatment or sclerotherapy, at the expense of increased encephalopathy, with no survival benefit.[68] Non-selective shunts resulted in similar outcomes compared with distal splenorenal shunts.[68] Extended follow-up of a randomised study comparing portocaval shunt surgery with sclerotherapy following acute variceal bleeding, reported better long-term bleeding control (100% vs 20%, p<0.001) and improved survival (5-year survival 71% vs 21%, p<0.001) in the portocaval shunt arm.[169] Distal splenorenal shunt surgery was compared with TIPSS in a multicentre RCT including 140 patients with Child's A and B cirrhosis.[170] Results showed similar rebleeding and survival, but higher rates of shunt dysfunction and re-intervention in the TIPSS group, although covered stents were not used. A follow-up study suggested that TIPSS was more cost-effective.[171]

Portosystemic shunts (total surgical, distal splenorenal or bare TIPSS) were compared with endoscopic therapy for variceal rebleeding in a Cochrane database systematic review.[172] Twenty-two trials incorporating 1409 patients were included. All shunt therapies reduced rebleeding (OR=0.24, 95% CI 0.18 to 0.30) at the expense of higher rates of encephalopathy (OR=2.09, 95% CI 1.20 to 3.62), with no survival advantage. TIPSS was complicated by a high incidence of shunt dysfunction.

Laparoscopic splenectomy plus VBL was also compared with TIPSS for variceal rebleeding in a recent non-randomised trial of 83 patients.[173] This reported surgery plus VBL to be better than TIPSS in preventing variceal rebleeding, with low rates of encephalopathy.

Liver transplantation should be considered in eligible patients following a variceal bleed determined by the selection criteria of the country.[174] There is no clear evidence that prior shunt surgery has a significant impact on transplant outcome.[169]

Recommendations for the secondary prophylaxis of variceal bleeding in cirrhosis are given below and in figure 3.

Recommendations: secondary prophylaxis of variceal haemorrhage in cirrhosis (figure 3)

1. Should VBL be used in combination with NSBB?
   1.1. NSBB (propranolol or nadolol)+VBL combination therapy are recommended as secondary prophylaxis (level 1a, grade A).
   1.2. NSBB or VBL monotherapy are suggested as alternative options taking into account patient preference and clinical judgement (level 1a, grade B).
   1.3. Carvedilol is suggested as an alternative to propranolol and nadolol (level 1b, grade B).
   1.4. If NSBB alone are used, there is no need to undertake further endoscopy unless clinically indicated (level 1a, grade A).
   1.5. We recommend that VBL alone is used to eradicate varices if there are contraindications or intolerance to combined use with NSBB (level 1a, grade A).
2. What is the optimal protocol for VBL?
   2.1. It is suggested that varices are banded at 2–4-weekly intervals until eradication (level 1b, grade B).
   2.2. After successful eradication of the varices, patients should be endoscoped at 3 months, then 6 monthly thereafter. Any recurrent varices should be treated with further VBL until eradication (level 1b, grade B).
   2.3. Proton pump inhibitors are not recommended unless otherwise required for peptic disease (level 1b, grade B).

3. When is TIPSS indicated?
   3.1. We suggest that TIPSS is used for patients who rebled despite combined VBL and NSBB therapy (or when monotherapy with VBL or NSBB is used owing to intolerance or contraindications to combination therapy), and in selected cases owing to patient choice. PTFE-covered stents are recommended (level 1a, grade A).
   3.2. Where TIPSS is not feasible in Child's A and B patients, we suggest shunt surgery can be used where local expertise and resources allow (level 1b, grade B).
4. Areas requiring further study:
   4.1. Combination of VBL and carvedilol (or other NSBB) versus carvedilol as monotherapy.
   4.2. Comparison of carvedilol with propranolol in secondary prophylaxis.
   4.3. Optimum time interval between VBL sessions.
   4.4. Strategy of VBL or NSBB discontinuation after variceal eradication during combination therapy with VBL +NSBB.
   4.5. Strategy of VBL add-on therapy to failure of NSBB monotherapy.
   4.6. Strategy of NSBB add-on therapy to failure of VBL monotherapy.
   4.7. Role of early TIPSS in secondary prophylaxis.
   4.8. Role of statins in secondary prophylaxis.
5. Quality indicator:
   5.1. Institution of secondary prophylaxis after acute variceal bleeding (level 1a, grade A)
   Numerator; patients with an acute variceal bleed who have received either NSBB or banding or both within 4 weeks of the index bleed.
   Denominator; patients with an acute variceal bleed.

GASTRIC VARICES
Natural history
At first endoscopy in patients with portal hypertension, 20% are shown to have gastric varices.[175] They are commonly seen in patients with portal hypertension due to portal or splenic vein obstruction.[175] Only 10–20% of all variceal bleeding occurs from gastric varices, but outcome is worse than with bleeding from oesophageal varices.[175][176]

Gastric varices can be classified on the basis of their location in the stomach and relationship with oesophageal varices. This classification has implications for management. The commonly used Sarin classification divides them into (a) gastro-oesophageal varices (GOV), which are associated with oesophageal varices; and (b) isolated gastric varices (IGV), which occur independently of oesophageal varices.[175] Both GOV and IGV are subdivided into two groups. Type 1 GOV are continuous with oesophageal varices and extend for 2–5 cm below the gastro-oesophageal junction along the lesser curvature of the stomach. Type 2 GOV extend beyond the gastro-oesophageal junction into the fundus of the stomach. Type 1 IGV refers to varices that occur in the fundus of the stomach and type 2 IGV describes varices anywhere else in the stomach, including the body, antrum and pylorus. The most common type of varices seen in cirrhosis is GOV type 1. Patients who bleed from IGV are at a significantly higher risk of dying from an episode of variceal bleeding than patients bleeding from GOV.[177]

Management of acute gastric variceal bleeding
Although no studies have reported the use of vasopressors and antibiotics specifically for the initial management of gastric variceal haemorrhage, any patient with suspected variceal bleeding

should be managed as described above (see section 'Management of active variceal haemorrhage'). Once endoscopy has identified the source of bleeding as gastric varices, therapeutic options include endoscopic methods, TIPSS, other radiological procedures, surgery and long-term NSBB. Splenic vein thrombosis should be considered and appropriate investigations undertaken in patients presenting with gastric variceal bleeding.

Endoscopic therapy
Endoscopic sclerotherapy
Sclerotherapy has been largely replaced by VBL and tissue adhesives or thrombin when appropriate for gastric varices, owing to the lower complication and rebleeding rates.

Endoscopic VBL
Standard VBL or the use of detachable snares has been shown to control active bleeding from gastric varices, but rebleeding and recurrence rates are high.[178][179] As GOV-1 are generally considered extensions of oesophageal varices, VBL is often used to treat bleeding from here. However, given the larger diameter and the anatomy of other types of gastric varices, and the limited data on use of VBL in this situation, this technique is generally not recommended for these.

Endoscopic injection therapy with tissue adhesives
Numerous studies have reported the use of tissue adhesives, most commonly histoacryl (N-butyl-cyanoacrylate), in the treatment of gastric varices.[180–194] Variations in technique, dilution with lipiodol and follow-up strategy have been described. These studies have reported an initial haemostasis success rate with tissue glue of 86–100%, with rebleeding rates of 7–28%. Uncommon, but severe complications, including emboli to the pulmonary and cerebral circulations, have been described.[181]

A randomised study compared cyanoacrylate injection with VBL in 60 patients with gastric variceal bleeding.[186] Patients treated with cyanoacrylate had a higher haemostasis rate (87% vs 45%), lower rebleeding (31% vs 54%) and lower mortality (29% vs 48%) than those treated with VBL. Another randomised study comparing cyanoacrylate with VBL in 97 patients with gastric variceal bleeding, reported equal haemostasis rates at 93%, but significantly higher rebleeding with VBL (72% vs 27%).[193] This study reported no difference in survival or complications between groups.

A non-randomised study comparing cyanoacrylate with VBL for gastric variceal bleeding reported similar haemostasis rates, but lower rebleeding with cyanoacrylate (32% vs 72%).[194] Survival and complication rates were similar in both groups. In a controlled but non-randomised study comparing cyanoacrylate with sclerotherapy for gastric variceal bleeding, Oho et al[188] showed that the haemostasis rate was significantly higher in the cyanoacrylate group. Survival was also significantly greater in patients treated with cyanoacrylate.

Mishra et al[187] reported a randomised study comparing cyanoacrylate injection with β blockers in the prevention of rebleeding in 67 patients with bleeding GOV-2 or IGV-1. During a median 26-month follow-up, patients in the cyanoacrylate group had significantly lower rates of both variceal rebleeding (15% vs 55%) and mortality (3% vs 25%). Treatment modality, presence of portal hypertensive gastropathy and gastric variceal size >20 mm correlated with mortality. Another recent RCT compared repeated gastric variceal obturation with or without NSBB in patients with bleeding GOV-2 or IGV-1.[182] Mortality and rebleeding rates were similar in the two

groups, although adverse effects were more common in the combination group.

In a non-randomised study, Lee et al[185] suggested that endoscopic ultrasound (EUS)-guided biweekly cyanoacrylate injection versus 'on demand' injection after recurrent bleeding led to significantly lower rebleeding (19% vs 45%) from gastric varices, although survival was similar. However, others have not confirmed this approach.[189] EUS-guided coil therapy has recently been described as having similar efficacy, but fewer adverse events, compared with cyanoacrylate injection in a small non-randomised study.[191]

Binmoeller et al[180] described a new method for the management of fundal gastric varices in 30 patients, using EUS and a combination of 2-octyl-cyanoacrylate and coils. Haemostasis was achieved in 100% of patients with no procedure-related complications. Use of coils appeared to reduce the volume of cyanoacrylate required to obliterate varices.

Endoscopic injection of thrombin

Injection of bovine thrombin to successfully control gastric variceal bleeding was initially described in a small cohort in 1994.[195] Varices were eradicated in all patients after a mean of two injections. Przemioslo et al[196] reported 94% haemostasis and 18% rebleeding in 52 patients with gastric variceal bleeding treated with bovine thrombin. Ramesh et al[197] also studied bovine thrombin for bleeding gastric varices. They reported 92% haemostasis, with no rebleeding during follow-up. No adverse events or technical problems were noted. More recent studies have used human rather than bovine thrombin because of safety concerns with the latter. McAvoy et al[198] reported on the largest series of patients treated with human thrombin injection for gastric or ectopic variceal bleeding. They reported 11% rebleeding in the 33 patients who had gastric variceal haemorrhage, with no significant adverse events. A recent series by Smith et al[199] reported a high rate of initial haemostasis in acute bleeding. However, failure to control bleeding or rebleeding was reported in >50%, suggesting that thrombin has a role in bridging to definitive treatment in acute bleeding. Where thrombin was used as prophylaxis, rebleeding occurred in 20%. To date, no randomised studies assessing thrombin injection for gastric variceal bleeding have been reported.

New endoscopic therapies

Two recent reports have described the successful use of Hemospray (Cook Medical, USA) in the management of active gastric variceal bleeding refractory to cyanoacrylate injection therapy.[200 201] In the latter case this was used as a bridge to a TIPSS procedure,[201] but in the former case TIPSS was not undertaken owing to pre-existing cardiomyopathy.[200] No rebleeding was reported in either case at a 30-day follow-up. Further data on the use of haemostatic powders in gastric variceal bleeding are required.

Balloon tamponade

Insertion of a Sengstaken–Blakemore or Linton–Nachlas tube may sometimes help to temporarily stabilise the patient with severe gastric variceal bleeding, which is uncontrolled by standard endoscopic methods as described above.[127] The Linton–Nachlas tube has been reported to have greater efficacy in gastric varices haemorrhage in a controlled trial.[128] However, rebleeding is almost universal if another treatment modality is not instituted.

Transjugular intrahepatic portosystemic stent-shunt

An initial TIPSS series using bare stents reported control of active bleeding from gastric varices in almost all patients in whom the shunt was performed successfully.[202–206] Tripathi et al[43] described 272 patients who had a TIPSS procedure for either gastric or oesophageal variceal bleeding. They reported similar rebleeding rates after TIPSS for either gastric or oesophageal varices. Initial PPG was lower in patients with bleeding from gastric varices. In addition, mortality was lower in those patients with initial PPG >12 mm Hg, who had TIPSS for gastric compared with oesophageal variceal bleeding. Shunt insufficiency and encephalopathy rates were similar in both groups. The authors suggested aiming to reduce HVPG to <7 mm Hg in gastric variceal bleeding.

Lo et al[207] undertook a randomised trial in 72 patients comparing TIPSS with cyanoacrylate injection in the prevention of gastric variceal rebleeding. Control of active bleeding had been achieved with cyanoacrylate in all patients before randomisation. They reported a significantly lower rate of gastric variceal rebleeding with TIPSS (11% vs 38%), although overall upper gastrointestinal rebleeding was similar in both groups. Encephalopathy was more common in those patients treated with TIPSS (26% vs 3%), but overall complications and survival were similar in both groups.

A non-randomised study compared TIPSS with cyanoacrylate injection for gastric variceal bleeding.[208] No differences were found in haemostasis, rebleeding or survival, but the group treated with TIPSS had increased encephalopathy. Another comparative study described lower rebleeding with TIPSS, but reduced in-patient length of stay with cyanoacrylate, and similar mortality.[209] This study also reported cyanoacrylate to be more cost-effective.

Other radiological procedures

The use of balloon-occluded retrograde transvenous obliteration (B-RTO) for the treatment of bleeding gastric varices was pioneered by the Japanese.[184 210] This procedure involves insertion of a balloon catheter into an outflow shunt (gastrorenal or gastric-inferior vena caval) via the femoral or internal jugular vein. Blood flow is blocked by balloon inflation, then the veins draining gastric varices are embolised with microcoils and a sclerosant injected to obliterate the varices.

In a small randomised study, B-RTO was compared with TIPSS in the management of 14 patients with active gastric variceal bleeding and gastrorenal shunts.[211] Immediate haemostasis, rebleeding and encephalopathy were similar in both groups. In a non-randomised study of 27 high-risk patients, Hong et al[212] compared B-RTO with cyanoacrylate injection in acute gastric variceal bleeding. Active bleeding at baseline was more common in the cyanoacrylate group. Haemostasis rates after B-RTO and cyanoacrylate were similar at 77% and 100%. Rebleeding was higher in the cyanoacrylate group (71% vs 15%), with complications and mortality similar in both groups. This rebleeding rate after cyanoacrylate is much higher than figures reported from other studies.

A large Korean retrospective study evaluated B-RTO for the management of gastric variceal haemorrhage.[213] Technical success of B-RTO was 97% with procedure-related complications seen in 4% and rebleeding in 22%. Another retrospective study of B-RTO for bleeding gastric varices described 95% technical success and 50% 5-year survival.[214] Cho et al[215] assessed B-RTO in 49 patients who had gastric varices with spontaneous gastro-systemic shunts. Procedural success rate was 84% but two procedure-related deaths occurred. No variceal recurrence or

rebleeding was noted. It has been reported that B-RTO can increase PPG and may aggravate pre-existing oesophageal varices and ascites.[215 216] Although B-RTO appears to be an effective alternative to TIPSS in patients with gastric variceal bleeding who have appropriate shunts,[217] it is rarely performed outside Asian centres.[218]

Percutaneous transhepatic variceal embolisation with cyano-acrylate and standard endoscopic cyanoacrylate injection have also been compared in a non-randomised study of 77 patients.[219] The authors reported lower rebleeding with the percutaneous approach, although mortality was similar in both groups.

Surgery

Surgery for portal hypertension should be performed by experienced surgeons in lower-risk patients, ideally in specialist units.[220] Because of the increasing use of simpler endoscopic and radiological procedures as described above, the need for such an intervention has reduced dramatically, and is mainly confined to splenectomy or splenic artery embolisation in patients with splenic vein thrombosis.[221 222]

Under-running of gastric varices has been shown to control active bleeding but is followed by recurrence of bleeding in 50% of patients and is associated with a perioperative mortality of >40%.[223] Complete devascularisation of the cardia, stomach and distal oesophagus for bleeding from gastric varices is associated with good control of bleeding but is followed by rebleeding in >40% of patients and early mortality in about 50%.[224] The use of distal splenorenal shunting for bleeding from gastric varices in patients with cirrhosis was reported in six patients with Child class A or B cirrhosis.[225] Although good control of bleeding was attained, two patients died in the postoperative period. Orloff et al[169] reported that a portal-systemic shunt can be an effective treatment for bleeding varices in patients with portal vein thrombosis and preserved liver function.

Primary prophylaxis of gastric variceal bleeding

A randomised study of 89 patients compared β blockers, cyano-acrylate injection and no active treatment in the primary prevention of bleeding from larger (>10 mm) GOV-2 and IGV-1.[226] Over a 26-month follow-up period, bleeding occurred in 38%, 10% and 53% of patients in the β blocker, cyanoacrylate and no-treatment groups, respectively. The cyanoacrylate group had significantly lower bleeding rates than the other groups for GOV-2, but not for IGV-1 patients. Mortality was lower in the group treated with cyanoacrylate (7%) than in those given no treatment (26%) but was similar to that in the β blocker group (17%). However, this was a small, single-centre study with an unusually high failure rate for NSBB. Many clinicians have significant concerns about the safety of cyanoacrylate injection in the context of primary prophylaxis.

In a retrospective study, Kang et al suggested that cyanoacrylate injection may be an effective prophylactic treatment for higher-risk gastric varices.[227]

A retrospective study evaluated the clinical outcomes of B-RTO for gastric varices, in which the procedure was performed as a primary prophylactic treatment in 40 patients.[228] The procedure was successful in 79% of patients, although procedural complications were reported in 9%. Survival at 1 and 5 years was 92% and 73%, respectively.

Recommendations: management of active haemorrhage from gastric varices (figure 3)

1. What is the optimal management of bleeding gastro-oesophageal varices?

1.1. GOV-1: treat as for oesophageal varices (level 2b, grade B).
1.2. GOV-2 and IGV:
  1.2.1. We recommend initial endoscopic therapy with cyanoacrylate injection (level 1a, grade A).
  1.2.2. Thrombin may also be considered (level 4, grade C).
1.3. TIPSS can be considered, depending on local resources and clinical judgement (level 3a, grade B).

2. In control of bleeding fails:
2.1. Balloon tamponade is suggested for GOV, IGV-1 until definitive treatment is undertaken (level 2b, grade B).
2.2. Salvage TIPSS is suggested as the first-line definite treatment, where feasible (level 3a, grade B).
2.3. B-RTO or surgical shunting can be considered if TIPSS is not possible (eg, portal vein thrombosis present) and depending on local resources (level 3a, grade B).

3. What are the therapeutic options for prevention of rebleeding from gastric varices?
3.1. We recommend that patients with GOV-1 are entered into a VBL surveillance programme (level 2b, grade B).
3.2. We recommend endoscopic surveillance with cyanoacrylate injection as needed for GOV-2 and IGV (note the optimum endoscopic follow-up strategy remains unclear)(level 2b, grade B). Thrombin can also be considered (level 4, grade C).
3.3. NSBB can be considered in certain circumstances after taking into account the patient's preferences and clinical judgement (level 1b, grade B).
3.4. We suggest TIPSS if patients rebleed despite cyanoacrylate injection. TIPSS can also be considered in other selected patients (eg, those with large or multiple gastric varices) (level 1b, grade B).
3.5. Shunt surgery may be used in selected patients with well-compensated cirrhosis and depending on local resources (level 3c, grade B).
3.6. Splenectomy or splenic artery embolisation should be considered in all patients where there is splenic vein thrombosis or left-sided portal hypertension (level 4, grade C).

4. Is there a role for primary prophylaxis of gastric variceal bleeding?
4.1. NSBB (level 2a, grade B) can be considered in selected high-risk patients with large GOV-2 after taking into account the patient's preferences and clinical judgement.
4.2. Cyanoacrylate injection is not recommended outside clinical trials (level 2a, grade A).

5. Areas requiring further study:
5.1. Role of thrombin in gastric varices, comparing this with tissue adhesives in both acute gastric variceal bleeding and secondary prophylaxis.
5.2. Role of TIPSS in acute gastric variceal bleeding and secondary prophylaxis.
5.3. Role of haemostatic powders in controlling refractory active gastric variceal bleeding.
5.4. Role of NSBB in the prevention of rebleeding from gastric varices.
5.5. Role of B-RTO as monotherapy or in combination with endoscopic injection of tissue adhesives in prevention of bleeding from gastric varices.
5.6. Role of EUS-guided injection of tissue adhesives or thrombin.
5.7. Primary prevention of gastric variceal bleeding with tissues adhesives and NSBB.

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