UPPER GASTROINTESTINAL HAEMORRHAGE
Supporting information

This guideline has been prepared with reference to the following:

NICE. Acute upper gastrointestinal bleeding: management. Clinical guideline: methods, evidence and recommendations. 2016. London. NICE

http://guidance.nice.org.uk/CG141

Recognition and assessment

The following groups of patients with acute upper GI haemorrhage are at high risk of needing surgery:

- **Systolic BP <100 mm Hg or postural hypotension at admission?**
- **Co-existing severe liver, cardiovascular, respiratory or renal disease?**
- **Re-bleeding following admission?**

A prospective, multi-centre, population based study of nearly 6,000 patients with acute upper GI haemorrhage (Rockall, 1996) has provided a predictive scoring system for mortality (and by implication, for preventative surgical intervention). The odds that death will occur are increased by the following factors:

- BP<100 = 2.43
- Liver failure = 2.84
- Cardiac failure = 2.06
- Pneumonia = 2.50
- Renal failure = 4.72
- Re-bleeding = 5.57

A Dutch study (Vreeburg, 1999) has confirmed the validity of the Rockall system for predicting mortality, but found that re-bleeding was not accurately predicted.
A prospective study comparing validity in the Rockall system as compared to the Baylor College system and the Cedars-Sinai Medical Centre predictive index (Camellini, 2004) found that all the systems had better discriminative ability for mortality than for re-bleeding. The Rockall accurately predicted re-bleeding in low and intermediate risk categories (< 6), but not in high risk categories.

Camellini L, Merighi A, Pagnini C, et al. Comparison of three different risk scoring systems in non-variceal upper gastrointestinal bleeding. Dig Liver Dis 2004;36:271-7

Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316-21
http://gut.bmj.com/content/38/3/316.long

Vreeburg EM, Terwee CB, Snel P, et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut 1999;44:331-5
http://gut.bmj.com/content/44/3/331.full

Evidence Level: III

Immediate treatment

Early GI endoscopy (within 24 hours) after acute upper GI haemorrhage will influence the clinical outcome?

A 2021 systematic review of 13 observational studies (with over 1.8 million patients) did not find evidence of a clear benefit of performing early GI endoscopy for acute upper GI haemorrhage (Azis, 2021). No significant difference in overall mortality (risk ratio: 0.97; CI, 0.74-1.27), recurrent bleeding (risk ratio: 1.12; CI, 0.62-2.00), and length of stay (SMD: -0.07, CI, -0.31 to 0.18) was observed for early endoscopy compared to later endoscopy. The possibility of endoscopic intervention was higher in the early endoscopy group (risk ratio: 1.70, CI, 1.28-2.27).
A 2021 systematic review compared the outcomes of “early” (within 24 hours) vs “very early” (within 12 hours) endoscopy (Merola, 2021). Five RCTs were identified with a total population of 926 cases. The meta-analysis showed no statistically significant benefit for very early endoscopy compared to early endoscopy in terms of risk of rebleeding, mortality, ICU admission, blood transfusion, surgery

and length of hospital stay. However, the results showed a significantly higher need for haemostatic treatment when very early endoscopy was performed (RR 1.23, 95% CI 1.06–1.42) in comparison to early endoscopy.

Aziz M, Dasari CS, Zafar Y et al. Does timing of endoscopy affect outcomes in patients with upper gastrointestinal bleeding: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2021;33:1055-62

Merola E, Michielan A & de Pretis G. Optimal timing of endoscopy for acute upper gastrointestinal bleeding: a systematic review and meta-analysis. Intern Emerg Med. 2021;16:1331-40

Evidence Level: I

No treatment (e.g. with H_2 RAs) is necessary prior to endoscopy

The use of pre-endoscopic intravenous proton pump inhibitors (PPIs) has been assessed in several studies. A meta-analysis of six RCTs comprising 2223 patients found that the use of these drugs before endoscopy is associated with both reduced high risk stigmata of bleeding and the need for endoscopic therapy (odds ratio [OR] 0.68, 95% confidence interval [CI] 0.50 to 0.93) but has no effect on patient outcomes, including rebleeding, need for surgery, or mortality (OR 1.12, 95% CI 0.72 to 1.73) [Sreedharan, 2010].

Prokinetic agents have been assessed for their ability to improve gastric emptying, thereby improving visualization at endoscopy. Erythromycin, usually given as a 250 mg infusion 30-120 minutes before endoscopy, has been most widely studied. The most recent meta-analysis of 598 patients in eight RCTs showed improved visualization, reduced need for second look endoscopy, and reduced length of hospital stay (mean difference −1.75 days, 2.43 to −1.06) after erythromycin infusion before endoscopy (Rahman, 2016). A 2023 Cochrane review found that when erythromycin was compared with placebo there was no evidence of a reduction in serious adverse events (risk difference (RD) −0.01, 95% CI −0.04 to 0.02; 3 studies, 255 participants), all-cause mortality (RD 0.00, 95% CI −0.03 to 0.03; 3 studies, 255 participants), non-serious adverse events (RD 0.01, 95% CI −0.03 to 0.05; 3 studies, 255 participants), or rebleeding (risk ratio (RR) 0.63, 95% CI 0.13 to 2.90; 2 studies, 195 participants) [Adão, 2023]. This review did find that erythromycin may improve gastric mucosa visualisation (mean difference (MD) 3.63 points on 16-point ordinal scale, 95% CI 2.20 to 5.05; 2 studies, 195 participants). It was also found that erythromycin may result in a slight reduction in blood transfusion (MD −0.44 standard units of blood, 95% CI −0.86 to −0.01; 3 studies, 255 participants).

Adão D, Gois AF, Pacheco RL et al. Erythromycin prior to endoscopy for acute upper gastrointestinal haemorrhage. Cochrane Database Syst Rev. 2023;2:CD013176
https://doi.org/10.1002/14651858.CD013176.pub2

Rahman R, Nguyen DL, Sohail U, et al. Pre-endoscopic erythromycin administration in upper gastrointestinal bleeding: an updated meta-analysis and systematic review. Ann Gastroenterol 2016;29:312-7
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923816/

Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev 2010;7:CD005415
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6769021/

Evidence Level: I

In patients with severe non-variceal bleeding, antihypertensives, diuretics, NSAIDs and anticoagulants should be stopped?

All of these groups of drugs are associated with varying degrees of risk of provoking or worsening gastrointestinal bleeding (Johnsen, 2001; Garcia Rodriguez, 1998; Suissa, 1998).

Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, et al. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998;158:33-9

Johnsen SP, Sorensen HT, Mellemkjoer L, et al. Hospitalisation for upper gastrointestinal bleeding associated with use of oral anticoagulants. Thromb Haemost 2001;86:563-8

Suissa S, Bourgault C, Barkun A, et al. Antihypertensive drugs and the risk of gastrointestinal bleeding. Am J Med 1998;105:230-5

Evidence Level: III

Is transfusion of red blood cells beneficial?
A 2019 review concluded that in most patients with upper gastrointestinal bleeding, red cell transfusion should be withheld until a hemoglobin threshold of 70-80 g/L is reached (Stanley, 2019). A Cochrane Review of 3 trials in a total of 126 patients (Jairath, 2010) concluded that "The studies in this review do not provide useful data regarding outcomes following red blood cell transfusion for acute upper gastrointestinal haemorrhage. They appear to exclude large survival benefit. Large, well-concealed RCTs of sufficient power are urgently needed."

Stanley AJ & Laine L. Management of acute upper gastrointestinal bleeding. BMJ 2019; 364:l536
https://www.bmj.com/content/364/bmj.l536

Jairath V, Hearnshaw S, Brunskill SJ, et al. Red cell transfusion for the management of upper gastrointestinal haemorrhage. Cochrane Database Syst Rev. 2010, Issue 9. Art. No.: CD006613
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006613.pub3/full

Evidence Level: I

Is antibiotic prophylaxis indicated in cirrhotic patients?
A Cochrane Review of 12 trials in a total of 1241 patients (Chavez-Tapia, 2010) found that "Antibiotic prophylaxis compared with no intervention or placebo was associated with beneficial effects on mortality (RR 0.79, 95% CI 0.63 to 0.98), mortality from bacterial infections (RR 0.43, 95% CI 0.19 to 0.97), bacterial infections (RR 0.36, 95% CI 0.27 to 0.49), rebleeding (RR 0.53, 95% CI 0.38 to 0.74), days of hospitalisation (MD -1.91, 95% CI -3.80 to -0.02), bacteraemia (RR 0.25, 95% CI 0.15 to 0.40), pneumonia (RR 0.45, 95% CI 0.27 to 0.75), spontaneous bacterial peritonitis (RR 0.29, 95% CI 0.15 to 0.57), and urinary tract infections (RR 0.23, 95% CI 0.12 to 0.41)."

Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010, Issue 9. Art. No.: CD002907
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002907.pub2/full

Evidence Level: I

Following acute upper GI haemorrhage, rapid restoration of blood volume with plasma expanders influences the clinical outcome?
Although IV saline is appropriate for restoring blood volume in many cases of upper GI haemorrhage, severe bleeding may necessitate the infusion of albumin or plasma expanders, or the transfusion of uncross-matched blood where oxygen-carrying capacity must be quickly restored (Jewell, 1996). Although blood volume must be restored to ensure cardiovascular stability, the means by which this is achieved appear not to be critical. A retrospective survey of 139 patients (Alexiu, 1975) found that 87.5% of 72 patients given large quantities (11 litres) of 0.9% saline and 5% glucose solution suffered no complications (other than reversible anaemia) compared with 73.1% of 69 patients given 2 litres of stored blood or colloid.
There is some evidence to suggest that Haemaccel may interfere with primary haemostasis, possibly due to its high calcium content (Evans, 1998).

Alexiu O, Mircea N, Balaban M, et al. Gastro-intestinal haemorrhage from peptic ulcer: an evaluation of bloodless transfusion and early surgery. Anaesthesia 1975;30:609-15

Evans PA, Glenn JR, Heptinstall S, et al. Effects of gelatin-based resuscitation fluids on platelet aggregation. Br J Anaesth 1998;81:198-202
http://bja.oxfordjournals.org/content/81/2/198.long

Jewell DP. Gastrointestinal bleeding. In: Weatherall DJ, Ledingham JG, Warrell DA (eds). Oxford Textbook of medicine, 3rd ed. Oxford: Oxford University Press, 1996. p1827

Evidence Level: V

Routine use of a central venous pressure line is unnecessary after acute GI haemorrhage except for patients with pre-existing cardiopulmonary disease or suspected variceal bleeding?

CVP measurements are useful in the prevention of cardiac overloading, and may be of value in preventing heart failure in patients with pre-existing cardiopulmonary disease (Northfield, 1970). An unexpected drop in CVP may also indicate rebleeding (Ghosh, 2002). National guidelines (Anon, 2002) recommend that a CVP line may be used in patients "who have significant cardiac disease" in order to clarify decisions about fluid replacement.

Anon. Non-variceal upper gastrointestinal haemorrhage: guidelines. British Society of Gastroenterology Endoscopy Committee. Gut 2002;51:iv1-iv6
http://gut.bmj.com/content/51/suppl_4/iv1.full

Ghosh S, Watts D, Kinnear M. Management of gastrointestinal haemorrhage. Postgrad Med J 2002;78:4-14
http://pmj.bmj.com/content/78/915/4.long

Northfield TC, Smith T. Central venous pressure in clinical management of acute gastrointestinal bleeding. Lancet 1970;ii:584-6

Evidence Level: V

Omeprazole 80 mg IV bolus injection followed by IV infusion at a rate of 8 mg/hr for 72 hours influences the clinical outcome?

A meta-analysis of 11 RCTs (Gisbert, 2001) showed that proton pump inhibitors (PPIs) are superior to H_2-receptor antagonists in the treatment of bleeding peptic ulcer. Persistent or recurrent bleeding was reported in 7% vs 13% of patients (OR 0.4; 95% CI 0.27-0.59). There was no statistically significant difference in requirement for surgery (OR 0.7) or in mortality (OR 0.7).

Another meta-analysis of 9 RCTs (Sharma, 2001) compared IV PPIs with either H_2RAs or placebo. Pooled rebleeding, surgery, and mortality rates were 13.2%, 8.9%, and 5.3% for PPIs, vs 17.5%, 12.4%, and 3.9% for H_2Ras and placebo. Odds ratios for rebleeding (0.71; 95% CI 0.55-0.92) and need for surgery (0.69; 95% CI 0.52-0.91) were statistically significant.

A further meta-analysis of 21 RCTs comprising 2915 patients (Leontiadis, 2005) came to similar conclusions, producing NNTs of 12 for reduced rebleeding and 20 for avoidance of surgery.

All-cause mortality was again found to be unaffected by PPI treatment (OR 1.02; 95% CI 0.76 – 1.37) in a meta-analysis of 26 trials in 4670 patients (Khuroo, 2005) and in a Cochrane Review of 6 trials in 2223 patients (Sreedharan, 2010).

Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010, Issue 7. Art. No.: CD005415
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005415.pub3/full

Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitors versus H_2-antagonists: a meta-analysis of its efficacy on bleeding peptic ulcer. Gastroenterology 2001;120:A247
http://onlinelibrary.wiley.com/enhanced/doi/10.1046/j.1365-2036.2001.01012.x/

Khuroo MS, Khuroo MS, Farahat KL, et al. Treatment with proton pump inhibitors in acute non-variceal upper gastrointestinal bleeding: a meta-analysis. J Gastroenterol Hepatol 2005;20:11-25
http://onlinelibrary.wiley.com/enhanced/doi/10.1111/j.1440-1746.2004.03441.x/

Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. BMJ 2005;330:568-70
http://www.bmj.com/content/330/7491/568

Sharma VK, Leontiadis GI, Howden CW. Intravenous proton pump inhibitors for peptic ulcer hemorrhage: meta-analysis of randomized controlled trials allowing endoscopic treatment. Gastroenterology 2001;120:A248

Evidence Level: I

In severe non-variceal bleeding, IV omeprazole should be given as an 80 mg bolus, followed by 8 mg/hr for 72 hrs, although this is an unlicensed dose?

A randomised, placebo-controlled trial of this strategy in 240 patients (Lau, 2000) found that bleeding recurred within 30 days in 8 patients in the omeprazole group (6.7%), vs 27 (22.5%) in the placebo group. Among the omeprazole group, 56 (46.7%) were hospitalised for less than 5 days, compared with 38 (31.7%) of the placebo group.

Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343:310-6
http://www.nejm.org/doi/full/10.1056/NEJM200008033430501#t=articleTop

Evidence Level: II

Transfer of patients likely to be fit for surgery to the care of a surgical team (once preliminary investigation and resuscitation is complete) influences the clinical outcome?
Typical postsurgical mortality in upper GI haemorrhage is between 8% - 9% (Thomopoulos, 1998). An audit of management of acute upper GI haemorrhage over one year at the Princess of Wales Hospital, Bridgend, Wales (Clements, 1991), revealed a low mortality rate of 4.6%, despite 68% of the 109 patients being over 60 and 17% being over 80. This was attributed to close co-operation between physicians and surgeons over agreed policy guidelines. These were based on early surgery for patients over 60 who re-bled from peptic ulcers (2 re-bleeds for under-60s), who required more than 4 units of blood products in 24 hours for volume replacement (more than 8 units for under 60s), or who showed a spurting vessel at endoscopy.

Clements D, Aslan S, Foster D, et al. Acute upper gastrointestinal haemorrhage in a district general hospital: audit of an agreed management policy. J R Coll Physicians Lond 1991;25:27-30

Thomopoulos K, Katsakoulis E, Vagianos C, et al. Causes and clinical outcome of acute upper gastrointestinal bleeding: a prospective analysis of 1534 cases. Int J Clin Pract 1998;52:547-50

Evidence Level: IV

Subsequent management

In patients aged over 60 years who require more than 4 units of whole blood to restore or maintain blood volume over 24 hours following an acute GI haemorrhage, or who continue to bleed, or who re-bleed, a surgical operation should be advised?
This advice corresponds to that given in national consensus guidelines (Anon, 2002), with the rider that repeat endoscopy may first be required, and that the decision whether or not to operate should be taken (based on the age and condition of the individual patient) by a consultant surgeon.

Anon. Non-variceal upper gastrointestinal haemorrhage: guidelines. British Society of Gastroenterology Endoscopy Committee. Gut 2002;51(Suppl IV):iv1-iv6
http://gut.bmj.com/content/51/suppl_4/iv1.full

Evidence Level: V

In patients aged under 60 years who require more than 8 units of whole blood to restore or maintain blood volume over 24 hours, or more than 12 units over 48 hours, or who show evidence of 2 episodes of re-bleeding, a surgical operation should be advised?
Please see evidence for previous question.

Evidence Level: V

In patients with acute upper GI haemorrhage resulting from bleeding oesophageal varices, intravenous terlipressin should be recommended as first line therapy pending upper GI endoscopy?
Evidence suggests that endoscopic therapy (sclerotherapy or band ligation) is the most effective way of controlling acutely bleeding oesophageal varices (Khuroo, 2005). These treatments, unlike the vasoactive drugs, are not always available in all hospitals, and may be difficult to apply in some patients. A vasoactive drug such as terlipressin may control an initial bleed and buy time pending endoscopy (Anon, 2000).
A Cochrane systematic review of 20 studies in 1609 patients (Ioannou, 2003) found a 34% RRR in mortality associated with the use of terlipressin and recommended it as the vasoactive agent of choice in acute variceal bleeding.
A randomised trial in 324 patients (Abid, 2009) compared terlipressin (n=163) with octreotide (n=161) as an adjuvant therapy to endoscopic management of variceal bleeding. Efficacy was similar for both

drugs, but those given terlipressin experienced a shorter length of stay in hospital: 108.40+/-34.81 vs 126.39+/-47.45 h (P< or =0.001).

Abid S, Jafri W, Hamid S, et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. Am J Gastroenterol 2009;104: 617-23
https://www.med.upenn.edu/gastro/documents/terlipressinvsoctreotide.pdf

Anon. Early management of bleeding oesophageal varices. Drug Ther Bull 2000;38:37-40

Ioannou G, Doust J, Rockey D. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev. 2003, Issue 1. Art. No.: CD002147
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002147/full

Khuroo MS, Khuroo MS, Farahat KL, et al. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. Aliment Pharmacol Ther 2005;21:347-61
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2005.02346.x/full

Evidence Level: I

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