Challenges in the management of acute peptic ulcer bleeding

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Acute upper gastrointestinal bleeding is a common medical emergency worldwide, a major cause of which are bleeding peptic ulcers. Endoscopic treatment and acid suppression with proton-pump inhibitors are cornerstones in the management of the disease, and both treatments have been shown to reduce mortality. The role of emergency surgery continues to diminish. In specialised centres, radiological intervention is increasingly used in patients with severe and recurrent bleeding who do not respond to endoscopic treatment. Despite these advances, mortality from the disorder has remained at around 10%. The disease often occurs in elderly patients with frequent comorbidities who use antiplatelet agents, non-steroidal anti-inflammatory drugs, and anticoagulants. The management of such patients, especially those at high cardiothrombotic risk who are on anticoagulants, is a challenge for clinicians. We summarise the published scientific literature about the management of patients with bleeding peptic ulcers, identify directions for future clinical research, and suggest how mortality can be reduced.

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Introduction

Acute upper gastrointestinal bleeding is characterised by fresh blood or coffee ground haematemesis and melaena (black tarry stool with a characteristic pungent odour). Anatomically, bleeding arises from a lesion proximal to the ligament of Treitz. In the 2007 UK National Audit, bleeding peptic ulcers accounted for 36% of all causes of acute upper gastrointestinal bleeding (table 1).[1] A systematic review reported an incidence of peptic ulcer bleeding that ranged from 19·4 to 57 per 100 000 population per year in 11 European studies.[2] In China, the prevalence of peptic ulcer bleeding has not been well studied, although peptic ulcer disease is common. In a cross-sectional endoscopic survey of 3600 volunteers in Shanghai with a mean age of 47·7 years, 17·2% of participants had peptic ulcer disease.[3] In two other hospital-based endoscopic surveys undertaken in Wuhan and Beijing,[4,5] the prevalence of peptic ulcer disease was 22·4% and 16·0%, respectively, and the rate of bleeding was estimated to be between 3·9% and 5·5%. In a country with a population of 1·33 billion people and with a *Helicobacter pylori* infection rate of 58%, the disease burden is high.[6] In this ageing population (the number of people aged >60 years will double in the next two decades) and with increasing urbanisation, the prevalence of coronary and cerebrovascular diseases will rise[7] and therefore so will the frequency of acute upper gastrointestinal bleeding related to use of aspirin and anticoagulants. In a cross-sectional survey of patients with aspirin and nonsteroidal anti-inflammatory drug-related acute upper gastrointestinal bleeding, investigators reported a low rate of adherence to gastro-protective drugs.[8]

Hospital admissions for peptic ulcer bleeding are declining ubiquitously because of reduced rates of *H pylori* infection (figure 1).[9–16] As evident from the two UK National Audits done in 1993 and 2007,[1,17] the mortality rate has improved from 14% to 10% in the period between the two audits, despite an unchanged age structure (median age 71 and 68 years, respectively). Mortality from bleeding peptic ulcers was 5·8% in 2007. Multicentre observational studies from the USA, Canada, and Italy reported similar mortality rates of 2·5, 5·4, and 4·9%, respectively.[14,18,19] The differences can be explained by how participants were sampled, their inclusion criteria, and definitions of case ascertainment.

Emergency surgery for bleeding peptic ulcers has continued to decrease; in the UK, the rate of surgery dropped from 8% to 2% between 1993 and 2006.[1,17] In the same period in the USA, admissions to hospital for peptic ulcer bleeding fell by 28·2%, the use of endoscopic treatment increased by 58·9%, and the rate of emergency ulcer surgery decreased by 21·9%.[20]

Initial assessment, resuscitation, and the use of blood products in patients with acute upper gastrointestinal bleeding

Patients presenting with acute upper gastrointestinal bleeding should be assessed promptly and resuscitated. Volume should be replenished initially with crystalloid solutions. In patients with ongoing blood loss, symptomatic anaemia, or those at increased risk of impaired tissue oxygenation (eg, patients with chronic heart conditions), blood should be transfused. In haemodynamically stable patients who are not bleeding actively, the threshold of transfusion needs to be defined. International guidelines recommend a policy of transfusion to a haemoglobin concentration of 7 g/dL.[21] From the recent UK National Audit, patients transfused within 12 h of their admissions had a twofold increase in rate of rebleeding and a 28% increase in mortality.[22] The

Search strategy and selection criteria

We searched PubMed, the Cochrane controlled clinical trial registry, and the Chinese language literature through China National Knowledge Infrastructure between January, 1990, and March, 2012. Search terms were "ulcer", "bleeding peptic ulcer", "gastrointestinal bleeding", "gastric ulcer", "duodenal ulcer", "epidemiology", "*H. pylori*", "non-steroidal anti-inflammatory drugs", "aspirin", and "proton pump inhibitor". We selected mostly randomised controlled studies and their meta-analyses, with the intention to address major aspects in the management of acute peptic ulcer bleeding. All selected studies were published in English or Chinese.

For more on **China National Knowledge Infrastructure** see http://www.global.cnki.net

	% (patients, n)
Peptic ulcer	36% (1826)
Oesophagitis	24% (1177)
Gastritis/erosions	22% (1091)
No abnormality seen	17% (865)
Duodenitis/erosions	13% (640)
Oesophagogastric varices	11% (544)
Mallory-Weiss tear	4·3% (213)
Malignancy	3·7% (187)
Total	5004

Data taken from the National United Kingdom Audit on acute upper gastrointestinal bleeding.[1]

Table 1: **Endoscopic diagnosis for patients presenting with acute upper gastrointestinal bleeding**

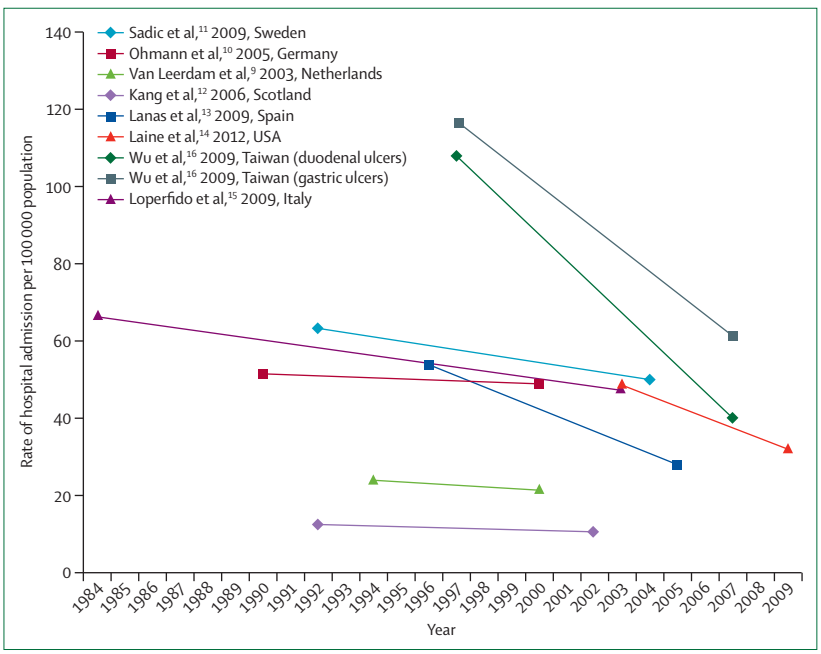

Figure 1: **Rate of admission to hospital for peptic ulcer bleeding per 100 000 population in recent time trend series**

Data taken from references 9–16.

increased rate of rebleeding was evident in all risk categories. The association between red cell transfusion and rebleeding and mortality might have been confounded by issues such as clinical evidence of bleeding. Because of the paradoxical outcomes, the UK National Blood Service is leading a national, cluster-randomised clinical trial (TRIGGER) to compare liberal and restrictive transfusion policies in patients with acute upper gastrointestinal bleeding.[23] In a recently published trial,[24] 921 patients with acute upper gastrointestinal bleeding were randomly allocated to receive transfusion to 7 g/dL (restrictive transfusion; 461 patients) or to 9 g/dL (liberal transfusion; 460 patients) and 225 (51%) and 65 (15%) patients in the two groups, respectively, did not receive transfusion. In patients who had restrictive transfusion, rebleeding was less common (10% *vs* 16%, p=0·01) and survival was higher at 6 weeks (95% *vs* 91%, hazard ratio 0·55, 95% CI 0·33–0·92, p=0·02) than in those in the liberal transfusion group. The difference in survival was mainly recorded in patients with liver cirrhosis in Child–Pugh class A and B. In the subgroup of patients with bleeding peptic ulcers, a trend towards less rebleeding (9% *vs* 12%, p=0·09) and a significant reduction in emergency surgery (2% *vs* 6%, p=0·04) were noted with restrictive transfusion. Less splanchnic blood flow and clotting derangement could explain these significant reductions in rebleeding and related deaths. The policy is generally applicable to stable patients with acute upper gastrointestinal bleeding.

Coagulopathy at presentation is a major adverse prognostic factor. From the UK National Audit,[25] coagulopathy defined by an international normalised ratio (INR) above 1·5 was present in 16·4% of patients and was associated with a 15% mortality rate (adjusted odds ratio 5·63, 95% CI 3·1–10·3). Coagulopathy is also a marker for comorbid illnesses, such as chronic liver disease. Bleeding in these patients is often more severe, and coagulopathy should be corrected in those with active bleeding. The target INR has not been defined and is established by the patient's indication for anticoagulation. A study showed that mild to moderate anticoagulation (INR 1·3–2·7) at endoscopy did not increase the risk of recurrent bleeding compared with an INR of less than 1·3.[26] One small cohort study with a historical comparison showed that aggressive resuscitation including correction of coagulation (INR <1·8) led to lower mortality rates.[27] Published data for the management of coagulopathy are scarce.

Risk scores in patients with acute upper gastrointestinal bleeding

Patients should be risk stratified at presentation. Clinical factors that predict a severe bleed and a need for urgent assessment include tachycardia, hypotension, nasogastric aspirate of red blood, and a haemoglobin concentration less than 8 g/dL.[28] Several scores for risk assessment have been published. The Rockall score is a composite score that combines pre-endoscopy clinical parameters and endoscopic findings to predict mortality.[29] The Glasgow Blatchford score[30] is calculated on the basis of clinical parameters alone. Both scores are used to predict the need for intervention. In a UK multicentre comparison[31] of the scores, the Glasgow Blatchford score was superior in predicting need for either endoscopic or surgical intervention (AUROC 0·85 *vs* 0·71, p<0·001). Although a high Glasgow Blatchford score (ie, score >1) has high sensitivity, its specificity is low, and a median score is therefore not useful to guide decisions in offering out-of-hours endoscopy. The Glasgow Blatchford score can accurately identify patients who do not need hospital admission

(ie, if Glasgow Blatchford score=0). The proportion of patients in this low-risk group is small, ranging from 5 to 22%. A large US study proposed a risk score to predict mortality, the AIMS65,[32] which is based on initial assessment of several clinical parameters (age, systolic blood pressure, mental status, INR, and albumin). The system needs further validation in other cohorts.

Early administration of proton-pump inhibitors

Early administration of intravenous proton-pump inhibitors in patients who present with signs of upper gastrointestinal bleeding is reasonable. A Cochrane meta-analysis of six randomised controlled trials (n=2223)[33] noted a reduction in high-risk stigmata of bleeding (37·2% *vs* 46·5%, odds ratio 0·67, 95% CI 0·54–0·84) with early use of proton-pump inhibitors and a lower proportion of patients undergoing endoscopic therapy (8·6% *vs* 11·7%, 0·68, 0·50–0·93). The meta-analysis did not show differences in other clinical outcomes. The reduction in endoscopic treatment leads to early discharge in some patients with clean-based ulcers and low-risk stigmata and is cost saving. However, the use of proton-pump inhibitors should not replace urgent endoscopy in patients with active bleeding.

The use of a prokinetic drug before endoscopy

A prokinetic drug given before endoscopy helps to empty stomach contents and improves viewing at endoscopy. These drugs are rarely used by endoscopists. Only five published randomised controlled trials and their pooled analysis have been published:[34] three trials of the use of erythromycin and two of metoclopramide. The use of these drugs reduces the need for a second endoscopic examination for diagnosis (OR 0·55, 95% CI 0·32–0·94). No significant difference in other clinical outcomes was recorded.

Endoscopic treatment: when, who to treat, and what to use

Endoscopy allows diagnosis of the cause of bleeding. Endoscopic stigmata of bleeding provide important prognostic information. More importantly, endoscopic treatment stops bleeding and reduces rates of continued or recurrent bleeding. In an early meta-analysis, endoscopic treatment was shown to reduce rebleeding (OR 0·38, 95% CI 0·32–0·45), surgery (0·36, 0·28–0·45), and mortality (0·55, 0·40–0·76).[35]

Patients with unstable haemodynamics and active haematemesis should be offered urgent endoscopy with a view to haemostasis. Patients who are stable after initial resuscitation generally undergo endsoscopy the next morning. Evidence for the use of early endoscopy (generally defined by endoscopy within 24 h) came from cohort studies and their meta-analysis.[36] Early endoscopy allows for discharge of patients at low risk of recurrent bleeding and leads to reduced hospital admission and resource use. Early endoscopy in high-risk patients potentially offers an opportunity to stop bleeding and improve clinical outcomes. Three small prospective randomised controlled studies[37–39] have compared urgent endoscopy (<6 h, <12 h, and cases defined as urgent) versus elective endoscopy (within 24 h or longer) in patients with acute upper gastrointestinal bleeding. Risk categorisation was poorly described. None of the trials showed any effect of urgent endoscopy on outcomes of recurrent bleeding, surgery, and death. The low mortality in the three trials suggests that low-risk patients were included in these studies.

The modified Forrest classification is often used to categorise endoscopic appearances of bleeding ulcers (I active bleeders; IIa visible vessel; IIb an adherent clot; IIc a flat pigmented spot; and III an ulcer with a clean base).[40] These signs predict risk of recurrent bleeding. Endoscopic treatment is indicated in ulcers with active bleeding or with a non-bleeding visible vessel or an adherent clot. Risks of recurrent bleeding without endoscopic treatment are 81% (I), 39% (II), and 22% (III). The published definition of an adherent clot varies. Conceptually, a clot should be contiguous with a breach in an artery. In a few patients, clot removal can be followed by profuse active bleeding. Two small randomised trials[41,42] and a meta-analysis[43] suggested that a clot should be removed in search of an artery and, when it is present, endoscopic treatment should be given.

Endoscopic treatment can be divided into injection, thermal, and mechanical methods. Injection of diluted adrenaline alone is now judged to be inadequate. Cushions of fluid injected into the submucosa compress the artery to stop or slow down bleeding and allow a clear view of the artery. A second modality should be added to induce thrombosis of the artery. Calvet and colleagues[44] pooled the results of 16 randomised controlled trials that compared injection of diluted adrenaline alone with injection followed by a second modality, and showed that combination treatment led to substantial reductions in rate of recurrent bleeding (risk reduction from 18·4% to 10·6%) and in surgery (from 11·3% to 7·6%) and mortality (from 5·1% to 2·6%). The investigators also compared studies with or without second look endoscopies after initial endoscopic treatment. Rebleeding was higher in the group given adrenaline injection alone (95 of 605, 15·7%) than in the combination treatment group (68 of 597, 11·4%). The observation suggested that if combination treatment had been instituted at index endoscopy, a second look endoscopy would not have been necessary. Two other meta-analyses that summarised studies of monotherapies versus dual therapies also concluded that a second modality should be added to injection treatment.[45,46] For monotherapy, either haemostatic clips or a thermal coaptive device should be used (figure 2), which have similar haemostatic efficacies.[47] Routine second look endoscopy after initial endoscopic haemostasis is not recommended. Meta-analyses of randomised controlled trials[48,49] suggested

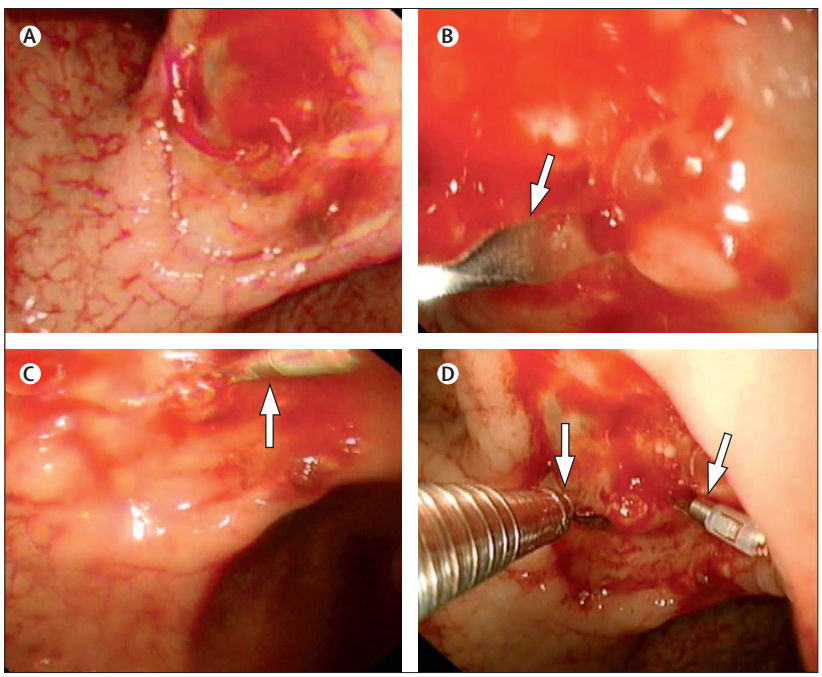

Figure 2: **Treatment of a bleeding gastric ulcer at the angular notch (Forrest type 1a bleeding)**
(A) A bleeding gastric ulcer at the angular notch. (B) An endoscopic clip was applied tangentially. (C) The first clip secured haemostasis, which stopped bleeding. (D) A second clip was then added. The clips are indicated by the white arrows.

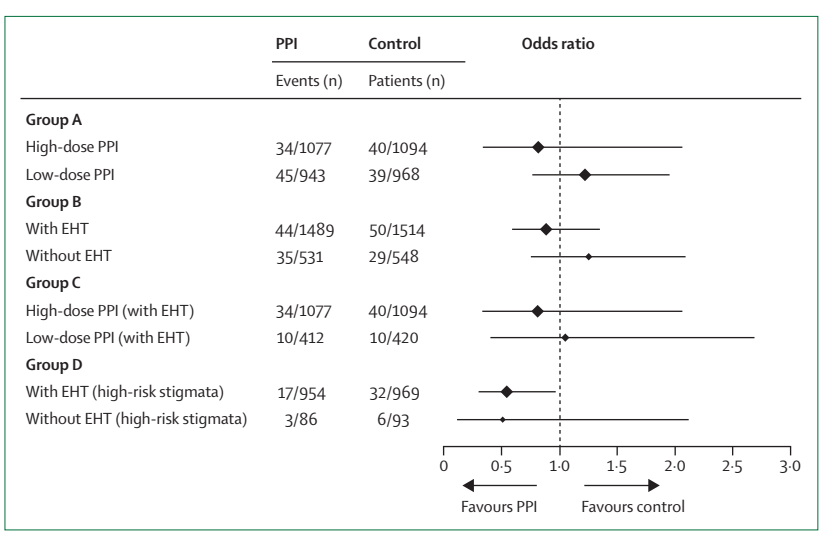

Figure 3: **Forrest plot to show efficacy of proton-pump inhibitors in reducing mortality in different subgroups**
(A) The use of high-dose versus low-dose PPI. (B) The use of PPI with or without endoscopic haemostatic treatment. (C) The use of high-dose or low-dose PPI in patients after EHT. (D) The use of PPI in patients with active bleeding and high-risk stigmata who received EHT. A significant reduction in mortality was seen in patients who received EHT for high-risk stigmata of bleeding (OR 0·54, 95% CI 0·3–0·96). Data taken from reference 50. PPI=proton-pump inhibitor. EHT=endoscopic haemostatic treatment.

only a modest reduction in the rate of recurrent bleeding (from 16·5% to 9·7%). Many of these trials used adrenaline injection alone and predated the use of proton-pump inhibitor infusion. In modern medical practice, the clinical benefits of routine second look endoscopy are probably small.

Acid suppression after endoscopic control

Gastric neutrality provides a favourable milieu for clot stability. To render gastric pH neutral, high-dose proton-pump inhibitors are needed. In a Cochrane systematic review of 24 trials and 4373 patients,[50] proton-pump inhibitor treatment was shown to reduce the rate of recurrent bleeding from 17·3% to 10·6% (OR 0·49; 95% CI 0·37–0·65) and the need for surgery from 9·3% to 6·1% (0·61, 0·48–0·78). The pooled mortality rate in the proton-pump inhibitor group was 3·9%, compared with 3·8% in the control group. A reduction in mortality with proton-pump inhibitor treatment was evident only in a subgroup analysis of 12 trials that included patients (954 patients on proton-pump inhibitors and 969 controls) with active bleeding or non-bleeding visible vessels to their ulcers after endoscopic haemostasis (1·78% *vs* 3·3%, OR 0·53, 95% CI 0·31–0·91; figure 3). These low rates of mortality in clinical trials suggest a selection bias. In one study[51] in which investigators compared proton-pump inhibitor treatment in a routine clinical practice with that in a clinical trial, the rate of rebleeding after proton-pump inhibitor treatment was 7·8% in the clinical practice and 5·9% in the clinical trial.

The optimum dose of proton-pump inhibitor after endoscopic haemostasis is controversial. An international multicentre placebo-controlled trial of 767 patients with high-risk bleeding ulcers reaffirmed that the use of high-dose esomeprazole reduced clinical rebleeding within 72 h from 10·3% to 5·9% (p=0·026).[52] Several randomised comparisons have been done between a high-dose infusion (80 mg bolus followed by an infusion of 8 mg per h) and a low-dose regimen (80 mg per day or less).[53,54] Some trials contained a small number of patients, had less optimum designs, and included patients with ulcers who harboured low-risk stigmata and even clean-base ulcers. In a meta-analysis from Taiwan[54] of these trials, investigators concluded equivalence between low-dose and high-dose regimens. Two more recent randomised controlled trials from Asia favoured the use of a high-dose regimen. A randomised controlled trial from Singapore[55] that enrolled consecutive patients after endoscopic haemostasis to their ulcers found a higher rebleeding rate with a low-dose than with a high-dose proton-pump inhibitor regimen (16% for low dose *vs* 3% for high dose). A single centre trial from China[56] in which 875 patients were randomly allocated to low or high doses of proton-pump inhibitors showed that the rate of rebleeding was lower in patients given a high dose (6·4% *vs* 11%, p=0·02). The use of a high-dose intravenous infusion could be suitable for patients who have undergone endoscopic haemostasis to their high-risk ulcers.

Use of antifibrinolytic drugs

Tranexamic acid, an antifibrinolytic drug, has been assessed for use in patients with acute upper gastrointestinal bleeding in seven trials and two meta-

analyses. In a meta-analysis of seven randomised controlled trials[42] comparing tranexamic acid with either placebo, histamine receptor antagonists, or proton-pump inhibitors, tranexamic acid reduced mortality rates (4·9% *vs* 8·2%, risk ratio 0·61, 95% CI 0·42–0·89) and surgery (8·8% *vs* 14·2%, 0·62, 0·35–1·09). Thromboembolic complications were higher with the use of tranexamic acid than with the other drugs tested (2·1% *vs* 1·1%). All except one of the randomised controlled trials were published in the 1970–80s. Two trials compared tranexamic acid with acid-suppressive drugs (cimetidine and lansoprazole) and one trial also provided endoscopic treatment. In the only trial[57] of endoscopic and PPI treatments, no difference in clinical outcomes was recorded. At present, insufficient evidence exists to support the use of tranexamic acid in acute upper gastrointestinal bleeding.

Continued and recurrent bleeding

In 8–15% of patients, endoscopy does not successfully control bleeding. Mortality after a surgical salvage in the recent UK National Audit was 29%.[58] Large ulcers located in the posterior bulbar duodenum and lesser curvature of stomach can erode into the gastroduodenal or the left gastric artery, respectively, which are predictive of endoscopic treatment failure. These ulcers often occur in elderly patients who present with a major bleed in shock and low initial haemoglobin concentrations.[59] We can divide these patients into two groups: those with massive bleeding in whom initial endoscopic control fails; and those with recurrent bleeding after endoscopic haemostasis.

Patients with massive bleeding who do not respond to primary control are often rushed to surgery. Angiographic embolisation is an alternative when its expertise is immediately available (figure 4). Loffroy and Guiu[60] summarised outcomes in ten case series of 75 patients treated with embolisation during a 17-year period. The rate of clinical success, rebleeding, and mortality rate was 75%, 25%, and 25%, respectively. Six retrospective comparisons have been done of angiographic embolisation to surgery in those who do not respond to endoscopic haemostatic attempts.[61–66] Angiographic embolisation was associated with reduced treatment-related complications (20–54% *vs* 37–68%). Mortality after either treatment was similar (3–30% *vs* 14–30%). In a pooled analysis, angiographic embolisation was associated with a substantially higher rate of recurrent bleeding (RR 2, 95% CI 1·36–2·94) than was surgery. A randomised controlled trial comparing both methods directly is ongoing (NCT 00766961).

Recurrent bleeding after initial endoscopic control occurs in 8–10% of cases. A randomised controlled trial compared surgery with further endoscopic treatment in these patients.[67] In 75% of patients, further endoscopic treatment led to durable haemostasis. Patients randomly allocated to surgery had substantially more postoperative complications. A subgroup analysis suggested that ulcers larger than 2 cm and a major rebleed with hypotension were factors that predicted failure in further endoscopic attempts. In smaller ulcers, the cause of bleeding might be related to suboptimal index endoscopic treatment. A second endoscopic attempt at haemostasis is worthwhile. In patients rebleeding from larger ulcers and in shock, surgery or angiographic embolisation should be immediately available if repeated endoscopic treatment fails.

An alternative approach is to pre-empt recurrent bleeding in patients predicted to be at high risk. One completed but unpublished and another ongoing randomised controlled trial (NCT 01125852 and NCT 01142180, respectively) are assessing the strategy of pre-emptive angiographic embolisation to bleeding ulcers after their initial endoscopic haemostasis. Results are eagerly awaited.

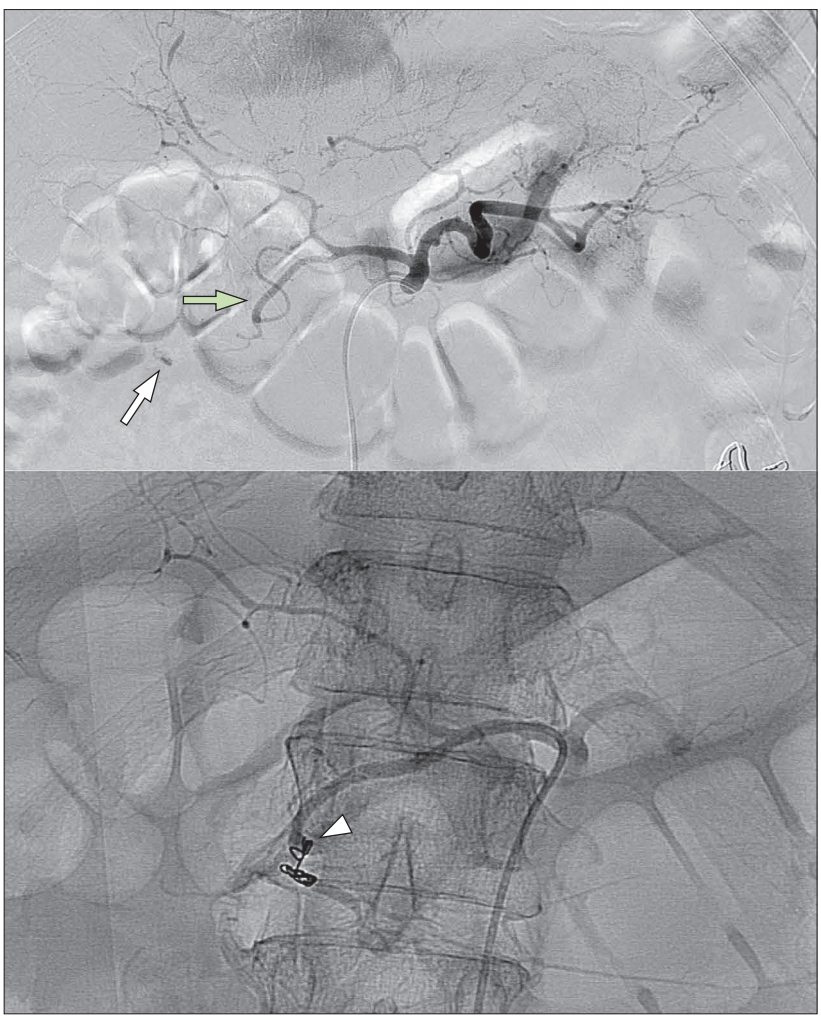

Figure 4: Radiographs showing active contrast extravasation (green arrow) from a branch of the gastroduodenal artery (white arrow) during angiography, and fibre coils that were deposited to the artery to stop bleeding (white arrowhead)

Management of bleeding in patients receiving anti-thrombotic treatment

Antithrombotic treatment includes the use of aspirin, other non-aspirin antiplatelet drugs, dipyridamole, thienopyridines, glycoprotein IIb/IIIa inhibitors, and anticoagulants. Newer anticoagulants targeting factor Xa and thrombin, such as dabigatran, apixaban, and rivaroxaban, are new drugs for stroke prevention in atrial fibrillation and for deep vein thrombosis. These drugs are particular challenges to clinicians because no antidotes exist for them. However, in two studies of human volunteers, infusion with prothrombin complex concentrates reversed coagulopathy induced by rivaroxaban and dabigatran, both in vivo and ex vivo.[68,69] For dabigatran, haemodialysis can also remove the drug effectively, especially in patients with poor renal function.

The management of patients on antithrombotic drugs complicated by acute upper gastrointestinal bleeding is a clinical dilemma. These patients have increased tendency of thromboembolism because of their underlying cardiovascular occlusive diseases. However, temporary cessation of anti-thrombotic therapy is often necessary to control bleeding or prevent early recurrent bleeding. The decision to withhold or resume anticoagulants should be multidisciplinary, and should be individualised, balancing thromboembolic risk against risk of recurrent bleeding.

In a randomised trial of continuous versus discontinued aspirin treatment in patients with bleeding peptic ulcers and high cardiothrombotic risks,[70] those receiving continuous aspirin had a twofold increased risk of early recurrent bleeding (10·3% *vs* 5·4% at day 30) but a tenfold reduced risk of all-cause mortality (1·3% *vs* 10·3% at 8 weeks) compared with those in whom aspirin was withheld. In patients at low risk of recurrent bleeding, aspirin can be resumed the next morning. The antiplatelet effect of aspirin lasts for about 5 days and the risk of early recurrent ulcer bleeding is high in the first 3 days; thus, it might be reasonable to resume aspirin on day 4 to minimise both bleeding and thrombotic risks, although some patients might receive active platelets in whole blood transfusion.

Patients on dual antiplatelet treatment are often at high risk of thrombosis, especially after recent placement of drug-eluting coronary stents. In patients at low risk of recurrent bleeding, dual antiplatelet treatment should be continued. In those at high risk, cessation of both antiplatelet drugs should be avoided. Cessation of antiplatelet treatment in the first month of implantation of drug-eluting coronary stents was associated with a hazard ratio of 161 for stent thrombosis.[71] Rate of stent thrombosis within 30 days in patients taking aspirin alone was 4·2% compared with 0·9% in those taking dual antiplatelet drugs.[72] According to a US database registry,[73] the median time to coronary stent thrombosis was as little as 7 days when both drugs were stopped, whereas it increased to 122 days if only clopidogrel was withheld. After endoscopic control of bleeding, we recommend high-dose proton-pump inhibitor infusion and temporarily withholding of clopidogrel. The antiplatelet activity of clopidogrel lasts for about 5 days. Early resumption of clopidogrel should be considered in patients who had stent placement within 4 weeks, left main stem disease, bifurcation stent, and known coronary artery dissection. Other risk factors include diabetes mellitus, renal failure, and depressed cardiac ejection fraction.

Major gastrointestinal bleeding is often associated with supratherapeutic doses of warfarin. Rapid correction of the coagulopathy is recommended. Intravenous vitamin K (5–10 mg) will reverse the coagulopathy but its full effect can take up to 24 h. Prothrombin complex concentrates rapidly reverse coagulopathy, and this treatment is preferred over fresh frozen plasma, especially in patients with cardiac and renal failure who tolerate fluid overloading poorly. Recombinant factor VIIa should be reserved only for patients with life-threatening bleeding. In a retrospective cohort study[74] of patients on warfarin treatment complicated by gastrointestinal bleeding, resumption of warfarin in the 90 days after the index bleed was associated with a lower risk for thrombosis (hazard ratio 0·05, 95% CI 0·01–0·58) and death (0·31, 0·15–0·62), without increasing the risk for recurrent bleeding (1·32, 0·50–3·57). The benefits of resumption of warfarin treatment outweigh its risks. In patients with high thrombotic risk, a bridging treatment with low-molecular-weight or unfractionated heparin should be considered. These high-risk patients include those with chronic atrial fibrillation and previous embolic events, a CHADS2 score[75] of 3 or higher, mechanical prosthetic heart valve, recent coronary event and deep vein thrombosis or pulmonary embolism, and patients with a hypercoagulable state, such as those with active cancer.

Patients with acute coronary syndrome are an especially high-risk group. Many receive several antithrombotic drugs, including potent glycoprotein IIb/IIIa receptor antagonists and short-acting direct thrombin inhibitors such as bivalirudin. These drugs are used in the context of coronary stent implantation, are of short duration, and treatment often cannot be stopped. In the ACUITY trial,[76] 1·3% of patients with acute coronary syndrome developed gastrointestinal bleeding with substantially higher 30-day mortality (9·6% *vs* 1·4%, p<0·0001). The rate of cardiac stent thrombosis was significantly higher than in patients without gastrointestinal bleeding (5·8% *vs* 2·4%, p=0·009). The optimum management strategy for these patients has not yet been defined. In the randomised REPLACE-2 trial, gastrointestinal bleeding occurred significantly more often in patients randomly allocated to receive heparin plus a glycoprotein IIb/IIIa-receptor inhibitor than in patients randomly allocated to receive bivalirudin (0·6% *vs* 0·1%, p=0·003).[77]

How to reduce mortality

The outcome of patients with acute upper gastrointestinal bleeding is affected by timing of endoscopy and quality of

endoscopic treatment in those who need it. The provision of care needs skill training, resource allocation, and organisation. From the UK National Audit, 17% of patients who died after admission did not receive an endoscopy. The UK National Patient Safety Agency identified failure to access care and endoscopic treatment as a source of morbidities and mortalities and subsequently issued a toolkit in attempts to strengthen organisational care and to improve safety and outcomes in patients with upper gastrointestinal bleeding.[78] The toolkit stipulates a consultant-led service and emphasises the importance of a local audit. Recommended service standards include patient risk assessment at presentation with a scoring system and early endoscopy to all patients, with urgent access to those at high risk. Endoscopy should be done by endoscopists competent in endoscopic treatments to both variceal and nonvariceal bleeding and assisted by trained nurses. The Agency also calls for establishment of upper gastrointestinal bleeding networks in regional services and secondary care in a larger referral hospital. This model could prove useful in many countries.

Endoscopic treatment will continue to evolve, with the aim to reduce initial failure to control bleeding and recurrent bleeding. A less skill-dependent drug for haemostasis could widen the general applicability of endoscopic haemostasis. We reported the first gastrointestinal use of a mineral blend haemostatic powder (Hemospray; Cook Medical, Winston-Salem, NC, USA) in 20 patients with actively bleeding

	Description of studies	Effect
Pre-endoscopy management		
Immediate assessment and resuscitation	One prospective cohort study,[27] aggressive resuscitation (shorter time to stable haemodynamics, to restore haematocrit >28% and INR<1·8)	Less myocardial infarction with aggressive resuscitation (5·6% *vs* 13·9%) and deaths (2·8% *vs* 11·1%); not statistically significant
Risk stratification	Several risk scores described: Rockall,[29] Blatchford,[30] AIMS65,[32] and others. Both Rockall and Blatchford extensively validated. Blatchford superior to Rockall in a multicentre UK study in prediction of endoscopic treatment and surgery[31]	The use of scores needs validation in individual institutions. Good for identification of low-risk patients for safe early discharge. Do not define a score beyond which urgent endoscopy becomes mandatory
Blood transfusion to patients actively bleeding, and blood transfusion to 7 g/dL in stable patients without chronic cardiac disorders such as ischaemic heart disease	Data from recent UK National Audit showed that early transfusion led to higher rate of recurrent bleeding in all risk categories as defined by the Rockall pre-endoscopy score.[22] One RCT[24]	A restrictive transfusion policy (transfusion when Hb<7 g/dL) led to less rebleeding (10% *vs* 16%, p=0·01) and better survival at 6 weeks (95% *vs* 91%, p=0·02) when compared with a liberal transfusion policy (transfusion when Hb<9 g/dL)
Correction of anticoagulation, and reversal of supratherapeutic warfarin in bleeding patients with prothrombin concentrates. Target INR (individualised), generally 1·5. Platelet transfusion to those with active bleeding and with a platelet count of <50 × 10⁹/L	International guidelines only. The cutoff INR is unknown. A cohort study of 233 patients indicated that rebleeding rate is not higher in patients with INR> 1·3[26]	Rebleeding in 23% of patients with INR>1·3 compared with 21% of those with INR<1·3
Use of prokinetic drugs	Meta-analysis of three RCTs and two abstracts (use of erythromycin in three and metoclopramide in two)	Reduction in the need for repeat endoscopy (29 of 162 *vs* 45 of 154; OR 0·55, 95% CI 0·32–0·94)
Early administration of PPI	Meta-analysis of six RCTs[33]	PPI treatment reduced endoscopic treatment (8·6% *vs* 11·7%; OR 0·68, 95% CI 0·5–0·93). No difference in mortality, rebleeding, or surgery
Endoscopic management		
Early endoscopy (24 h)	Recommendations by an international guideline,[21] and assessed in a meta-analysis and cohort studies.[36] Three small RCTs compared urgent with early elective endoscopies[37-39]	Reduced hospital resource use in low-risk patients. Improvement in clinical outcomes less certain. No difference in mortality (2 of 265 *vs* 3 of 263). Low rate of mortality suggested inclusion of low-risk patients
Endoscopic treatment of Forrest I and IIa ulcers	Early meta-analyses of RCTs[35] and a recent pooled analysis[40]	Early meta-analysis suggested reduction in recurrent bleeding or surgery and deaths. Data from latest pooled analysis[40] showed a substantial and statistically significant reduction in recurrent bleeding with both active bleeding (RR 0·29, 95% CI 0·20–0·43) and non-bleeding visible vessels (0·49, 0·40–0·59). Substantial reduction in surgery and fewer deaths (not statistically significant). RR for death in those with active bleeding 1·28 (95% CI 0·26–6·21) and pooled rate of deaths 2/68 (3%) in those without endoscopic therapy. RR for death in those with non-bleeding visible vessles 0·62 (0·36–1·06) and pooled rate of deaths 30/441 (7%) in those without endoscopic therapy
Endoscopic treatment of ulcers with clots	Two small RCTs and their meta-analysis that included published abstracts and a subgroup analysis from another RCT[41-43]	Rebleeding less frequent with endoscopic treatment than with medical treatment alone (5 of 61 [8·2%] *vs* 21 of 85 [24·7%]). No difference in other clinical outcomes
Injection of diluted adrenaline alone is not optimum; a second modality should be added	Three meta-analyses[44-46]	All meta-analyses suggested significant reduction in rate of recurrent bleeding and surgery. One study also showed a significant reduction in mortality (from 5·1% to 2·6%; OR 0·51, 95% CI 0·31–0·84)[44]
Clips and thermocoagulation are similar in their haemostatic efficacies	Meta-analyses of RCTs[46,47]	Rate of definitive haemostasis (81·5% *vs* 81·2%; RR 1, 95% CI 0·77–1·31) in one meta-analysis[47]

(Continues on next page)

	Description of studies	Effect
(Continued from previous page)		
Post-endoscopic management		
Use of PPI after endoscopic therapy	Meta-analysis of RCTs[50]	PPI treatment reduced rebleeding (OR 0·49, 95% CI 0·37–0·46) and need for surgery (0·61, 0·48–0·78). In a subgroup analysis of patients with active bleeding and non-bleeding visible vessels who received endoscopic haemostatic treatment, addition of PPI treatment reduced mortality (0·53, 0·31–0·91)
High-dose *vs* low-dose PPI	A meta-analysis of RCTs with inclusion of patients with low-risk stigmata of bleeding.[54] Two subsequent RCTs favoured the use of high-dose regimens[55,56]	Less rebleeding with high dose in both trials: 3 of 61 *vs* 10 of 61,[55] and 6·4% *vs* 11% of 875 patients[56]
The use of tranexamic acid	Seven RCTs and two meta-analyses.[88] Two studies used acid suppression (cimetidine and lansoprazole) and one study also used endoscopic treatment	In the most recent meta-analysis,[88] tranexamic acid reduced mortality compared with placebo (41 of 829 *vs* 68 of 825; RR 0·61, 95% CI 0·42–0·89). In one trial that compared tranexamic acid with PPI and endoscopic treatments, no difference in clinical outcomes noted[57]
Routine second look endoscopy	Two meta-analyses of RCTs.[48,49] Most trials predated intensive PPI treatment and used epinephrine injection alone	One meta-analysis[49] showed reduction in rate of recurrent bleeding (OR 0·55, 95% CI 0·37–0·81) and surgery (0·43, 0·19–0·96). No difference in mortality. In modern practice, benefit of routine second look endoscopies is likely to be small
Patients on antithrombotics		
Aspirin alone	One RCT of 156 patients on immediate resumption of aspirin[70]	More rebleeding with continuation of aspirin (10·3% *vs* 5·4%); substantially more deaths at 8 weeks (10·3% *vs* 1·3%) with withholding of aspirin
Use of aspirin and clopidogrel	Prospective cohort study[72]	High risk of coronary stent thrombosis if both drugs stopped. Stent thrombosis rate within 30 days of implantation of drug-eluting stents on thienopyridine was 0·9% compared with 4·2% in those without thienopyridine. In patients at low risk of recurrent bleeding from their ulcers, such as those with clean base ulcers or ulcers with minor stigmata of bleeding, dual antiplatelet drugs should be continued. Patients at moderate-to-high risk of recurrent bleeding should remain on at least one antiplatelet drug
Warfarin and other anticoagulants	Retrospective cohort study[74]	Management of such patients should be individualised, and thrombotic risks balanced against rebleeding risks from their ulcers. Multidisciplinary input should be sought. In patients at high thrombotic risk (eg, those with mechanical heart valves or recent thrombotic events), a bridging therapy with intravenous heparin should be considered. Resumption of anticoagulant treatment led to fewer thrombotic events (0·4% in 260 *vs* 5·5% in 182, HR 0·05, 95% CI 0·01–0·58) and fewer deaths (5·8% *vs* 20·3%, p<0·001) in 90 days without significantly increased risk of gastrointestinal bleeding (10 *vs* 5·5%, p=0·09)
Management of continued or recurrent bleeding		
Further endoscopic treatment *vs* surgery	One RCT[67]	In 35 of 48 patients, endoscopic retreatment was successful. With ITT analysis, complications were higher in the surgery group than in the further endoscopic treatment group (16 of 44 *vs* 7 of 48, p=0·03). Mortality high in both groups 5 of 48 *vs* 8 of 44, p=0·37). Shock and ulcer size >2 cm predicted failure to endoscopic retreatment
Angiographic embolisation *vs* surgery	Six retrospective comparative studies,[61–66] and one ongoing RCT (NCT 00766961)	No difference in mortality. Higher rate of recurrent bleeding with angiography (RR 2, 95% CI 1·3–2·9, p<0·001)
Role of pre-emptive angiographic embolisation	One completed RCT (NCT 01125852) and one ongoing RCT (NCT 01142180); both unpublished	Uncertain

INR=international normalised ratio. RCT=randomised controlled trial. RR=risk ratio. OR=odds ratio. PPI=proton-pump inhibitor. HR=hazard ratio. ITT=intention to treat.

Table 2: **Summary of treatments for patients with acute nonvariceal upper gastrointestinal bleeding, description of studies for each treatment, and their effects**

ulcers and achieved haemostasis in 19 of them.[79] Haemostatic clips continue to evolve. We now have more secure clips that capture larger amounts of tissue.

Future research should focus on subgroups of patients at high risk of continued or recurrent bleeding. The associated increase in mortality is at least fourfold. These include patients who are anticoagulated for their medical comorbidities or patients with ulcers who are predicted to not respond to endoscopic treatment. Accurate prediction of those patients who are not likely to respond to endoscopic treatment and their early treatment could prevent recurrent bleeding. Organ support and management of their comorbid illnesses, including antithrombotic treatments, are crucial elements of the care for these patients.

A reduction in mortality from peptic ulcer bleeding will probably arise from prevention of peptic ulcer bleeding. The American College of Cardiology Foundation, the College of Gastroenterology, and the Heart Association issued joint statements[80,81] about how to reduce the gastrointestinal risks of antiplatelet treatment and nonsteroidal anti-inflammatory drugs. In patients who need antiplatelet treatment, proton-pump inhibitor cotreatment is indicated in those with a history of uncomplicated or complicated peptic ulcer disease, who need dual antiplatelet drugs or concomitant

anticoagulation treatment. Patients with a history of peptic ulcers should be tested for *H pylori* and treated if infection is present. Additionally, the panel recommended proton-pump inhibitor cotreatment in patients older than 60 years, on non-steroidal anti-inflammatory drugs or corticosteroids, or those with dyspepsia or reflux symptoms. The efficacy of proton-pump inhibitor gastroprotection in nonsteroidal anti-inflammatory drug users depends on adherence to treatment. In a large international primary care study,[82] every 10% reduction in adherence increased the risk of an upper gastrointestinal bleed by 9%. Concomitant use of proton-pump inhibitors might competitively inhibit activation of clopidogrel by CYP2C19 and increase cardiovascular risks. However, the only available randomised trial[83] showed no notable association between omeprazole and cardiovascular events, and suggested that omeprazole significantly protected against gastrointestinal events. Because of the plausible biological interaction and the supporting pharmacodynamic data, omeprazole should probably be avoided in patients who need clopidogrel.

We now have effective strategies in secondary prophylaxis. In patients with *H pylori*-associated ulcer disease, eradication treatment is significantly more effective than is long-term maintenance antisecretory treatment with proton-pump inhibitors or histamine-2 receptor antagonists.[84] In nonsteroidal anti-inflammatory drug users, combination treatment with misoprostol, proton-pump inhibitors, and double-dose histamine receptor antagonist or use of COX-2-selective inhibitors decreases endoscopic ulcers in patients who continue to need nonsteroidal anti-inflammatory drugs.[85] In patients at very high risk of recurrent bleeding, we showed that the combined use of a proton-pump inhibitor and celecoxib was better than celecoxib alone in the prevention of recurrent ulcer bleeding (0% *vs* 8·9% at 13 months, p<0·001).[86] Patients with idiopathic ulcers not caused by *H pylori* or nonsteroidal anti-inflammatory drugs have a high rate of recurrence and mortality.[87] An antisecretory drug should be prescribed to prevent recurrences.

Conclusions

The management of patients with acute upper gastrointestinal bleeding can be divided into three phases: before, during, and after endoscopic treatment. Table 2 summarises treatments at these phases, studies supporting their use, and effects on patient outcomes. Timely endoscopic haemostatic treatment and acid suppression are crucial in the successful management of patients with bleeding peptic ulcers. The care of these patients is becoming increasingly multidisciplinary. Management of their comorbid illnesses, and in many patients, antithrombotic drugs, becomes an integral component of care. Patients at high risk of continued or recurrent bleeding should be identified. Future clinical research should focus on these patients, with the aim to improve their outcomes.

Contributors

JYWL and FKLC reviewed the relevant scientific literature and wrote the report. AB, EJK, D-mF, and Y-sY critically reviewed and approved the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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