Review

Multidisciplinary management strategies for acute non-variceal upper gastrointestinal bleeding

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Background: **The modern management of acute non-variceal upper gastrointestinal bleeding is centred on endoscopy, with recourse to interventional radiology and surgery in refractory cases. The appropriate use of intervention to optimize outcomes is reviewed.**

Methods: **A literature search was undertaken of PubMed and the Cochrane Central Register of Controlled Trials between January 1990 and April 2013 using validated search terms (with restrictions) relevant to upper gastrointestinal bleeding.**

Results: **Appropriate and adequate resuscitation, and risk stratification using validated scores should be initiated at diagnosis. Coagulopathy should be corrected along with blood transfusions, aiming for an international normalized ratio of less than 2·5 to proceed with possible endoscopic haemostasis and a haemoglobin level of 70 g/l (excluding patients with severe bleeding or ischaemia). Prokinetics and proton pump inhibitors (PPIs) can be administered while awaiting endoscopy, although they do not affect rebleeding, surgery or mortality rates. Endoscopic haemostasis using thermal or mechanical therapies alone or in combination with injection should be used in all patients with high-risk stigmata (Forrest I–IIb) within 24 h of presentation (possibly within 12 h if there is severe bleeding), followed by a 72-h intravenous infusion of PPI that has been shown to decrease further rebleeding, surgery and mortality. A second attempt at endoscopic haemostasis is generally made in patients with rebleeding. Uncontrolled bleeding should be treated with targeted or empirical transcatheter arterial embolization. Surgical intervention is required in the event of failure of endoscopic and radiological measures. Secondary PPI prophylaxis when indicated and *Helicobacter pylori* eradication are necessary to decrease recurrent bleeding, keeping in mind the increased false-negative testing rates in the setting of acute bleeding.**

Conclusion: **An evidence-based approach with multidisciplinary collaboration is required to optimize outcomes of patients presenting with acute non-variceal upper gastrointestinal bleeding.**

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Introduction

Upper gastrointestinal bleeding (UGIB) is defined as bleeding proximal to the ligament of Treitz. Patients may present with overt bright red blood or 'coffee ground' haematemesis, melaena or haematochezia. The incidence of acute UGIB ranges from 50 to 150 per 100 000 adults per year, with a mortality rate of 2·5–10 per cent, although there have been recent reports of decreasing rates of hospital admission and mortality[1,2]. Nonetheless, the burden on healthcare expenditure remains significant. A UK national audit[3] of UGIB further reported rebleeding rates of 11·9 per cent. Overall, 2·3 per cent of patients required surgery and 1·3 per cent underwent transcatheter arterial embolization (TAE) for non-variceal UGIB (NVUGIB). Some 10–24 per cent of patients have bleeding attributable to a variceal source or portal gastropathy[1,4,5], which carries a higher mortality rate and differs in terms of management, and is beyond the scope of this review. Peptic ulcers remain, in many areas, the most common cause of UGIB, with an array of additional possible findings (*Table 1*)[1,6–11]. A large portion of the evidence in UGIB is derived from the peptic ulcer bleeding literature. In clinical practice, this is often extended to patients with non-ulcer bleeding.

Table 1 Lesions identified at endoscopy for non-variceal upper gastrointestinal bleeding from selected multicentre bleeding registries

	UK UGIB audit[6]	RUGBE[7]	CORI[8]	PNED[9]	REASON[10]	UK bleeding registry[1]	ENERGiB[11]
Year	1993	1999–2002	2000–2004	2003–2009	2004–2005	2007	2008
Study type	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective
Country	UK	Canada	USA	Italy	Canada	UK	Seven European countries*
No. of sites	74	18	72	36	21	208	123
No. of patients	4185	1869	11 160	3207	1805	5004	2660
Lesion (%)†							
Ulcer	35	56	32·7	63·8	63·1	36	63·5
Erosion	11	10	18·8	9·9	22·2	22	19·5‡
Oesophagitis	10	9	n.a.	5·8	22·6	24	11
Mallory–Weiss tear	5	n.a.	4	4·6	7·4	4·3	n.a.
Malignancy	4	n.a.	1·2	4·8	2·6	3·7	n.a.
Other	6	n.a.	n.a.	4·5§	4·6¶	2·6#	n.a.
No findings	25	3·6	17·2	n.a.	n.a.	17	n.a.
Variceal bleeding	4	No	No	No	No	11	No

*Belgium, Greece, Italy, Norway, Portugal, Spain and Turkey. †More than one lesion possible in a single patient. ‡Including gastritis, gastric erosions and erosive duodenitis; §Dieulafoy and vascular lesions; ¶Dieulafoy and gastric antral vascular ectasia; #arteriovenous malformation, vascular ectasia and haemobilia. UGIB, upper gastrointestinal bleeding; RUGBE, Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy; CORI, Clinical Outcomes Research Initiative; PNED, Progetto Nazionale Emorragie Digestive; REASON, Registry of Patients Undergoing Endoscopy and/or Acid Suppression Therapy and an Outcomes Analysis for Upper Gastrointestinal Bleeding; ENERGiB, European Survey of Non-Variceal Upper Gastro Intestinal Bleeding; n.a., data not available.

The management of patients with UGIB is centred on proper resuscitation, leading to early endoscopy with appropriate haemostasis for high-risk cases. Despite the widespread use of endoscopic and adjuvant acid-suppressive therapy, approximately 13 per cent of patients in a real-life setting experience rebleeding[3,7], which in itself is associated with increased mortality[12]. Predictors of rebleeding after endoscopic haemostasis include haemodynamic instability, active bleeding at endoscopy, ulcer size over 2 cm, ulcer location in high lesser gastric curvature or posterior duodenum, haemoglobin level less than 100 g/l and the need for transfusion[13].

Therapeutic options in the setting of rebleeding include repeat endoscopic haemostasis, TAE and surgery. The role of each is reviewed below, although the optimal management strategy needs to be individualized and calls upon multidisciplinary expertise.

Methods

A search of PubMed and the Cochrane Central Register of Controlled Trials between January 1990 and April 2013 was conducted with the following search terms: 'ulcer', 'bleeding peptic ulcer', 'gastrointestinal bleeding', 'gastric ulcer', 'duodenal ulcer', 'epidemiology', '*H. pylori*', 'endoscopy', 'aspirin', 'proton pump inhibitor', 'transcatheter arterial embolization' and 'surgery'. All selected studies were published in English. Where possible the inclusion of randomized clinical studies and their meta-analyses was prioritized. Where these were not available, key observational studies were selected and complemented with personal experiences and unpublished data where appropriate, with the intention of addressing major aspects in the management of UGIB and focusing on the emergency management of refractory bleeding.

Presentation and diagnosis

The evaluation of patients presenting with gastrointestinal bleeding starts by establishing the source of haemorrhage (upper *versus* lower). Although haematemesis and melaena suggest a more proximal source, 15 per cent of patients with UGIB present with haematochezia[14]. Predictors of an upper gastrointestinal source include melaena on history (range of positive likelihood ratios (LRs) 5·1–5·9) or on examination (positive LR 25, 95 per cent confidence interval (c.i.) 4 to 174), nasogastric lavage with 'coffee grounds' or blood (positive LR 9·6, 4·0 to 23·0) and a serum urea nitrogen to creatinine ratio above 30 (positive LR 7·5, 2·8 to 12·0)[15]. Furthermore, a variceal source should be considered if there is a history of liver disease, cirrhosis or excessive alcohol use, haematemesis or haematochezia, or if examination reveals stigmata of chronic liver disease[4], as the management of variceal bleeding differs. A non-variceal source of UGIB is seen not infrequently in patients with cirrhosis; among 468 patients with cirrhosis in a prospective population-based study[16], 59 per cent had bleeding from varices and 16 per cent from peptic ulcers, whereas Villanueva and colleagues[5] reported rates of 76 and 14 per cent respectively.

Resuscitation, transfusion and coagulopathy

In addition to providing adequate fluid resuscitation, blood transfusions should be considered in patients with haemoglobin levels below 70 g/l. This threshold for transfusion is associated with decreased in-hospital mortality in the critically ill patient without significant volume depletion due to bleeding[17]. Recently validated in 921 patients with UGIB, a restrictive strategy aiming for a haemoglobin level between 70 and 90 g/l, compared with a more liberal target of 90–110 g/l, resulted in improved 6-week survival rates (95 *versus* 91 per cent; hazard ratio (HR) 0·55, 95 per cent c.i. 0·33 to 0·92) and reduced bleeding (10 *versus* 16 per cent; adjusted HR 0·68, 0·47 to 0·98). Significant benefits were restricted to patients with cirrhosis of limited severity (Child–Pugh grade A or B). Among patients with bleeding peptic ulcer, except for a significant decrease in the need for surgery, only trends towards improved survival and rebleeding were noted[5]. Keeping in mind the exclusion criteria applied in the studies when generalizing the results, patients with massive bleeding or ischaemia (acute coronary syndrome, symptomatic peripheral vasculopathy, stroke or transient ischaemic attack) are likely to benefit from earlier transfusions.

Observational data have shown a twofold increase in rebleeding in those requiring early transfusion (within 12 h[18] to 24 h[19]), and trends towards increased mortality[18,20], after adjustment. A recently completed UK multicentre trial comparing restrictive *versus* liberal strategies (80 *versus* 100 g/l haemoglobin as target values) in UGIB will provide additional evidence, specifically in patients with NVUGIB[21]. Evidence-based recommendations for a well defined platelet transfusion threshold are lacking, although some suggest maintaining platelet counts above 50×10^9/l (100×10^9/l if impaired function is suspected); the range of platelet levels usually encountered in NVUGIB does not seem to predict either rebleeding or mortality[22].

The presence of coagulopathy should be corrected without delaying endoscopy[23]. Endoscopic haemostasis can be achieved successfully despite international normalized ratio (INR) levels between 1·5 and 2·5 after correction, as suggested by a case–control study[24] showing subsequent rebleeding rates unchanged by values up to 2·7[25]. A presenting INR above 1·5 is, however, a predictor of death but not rebleeding, perhaps acting as a proxy for the presence of co-morbid conditions[26], although others[3] have suggested an association with rebleeding. New oral anticoagulants increase the risk of gastrointestinal bleeding[27], and represent a challenge in acute UGIB management as there are no currently approved reversal agents[28].

Risk stratification

Early stratification of patients into high- and low-risk categories using clinical, laboratory and endoscopic findings allows the identification of individuals who may benefit from earlier interventions and closer monitoring over the first 72 h[29], and those who can safely be discharged after endoscopy[23]. Predictors of severe UGIB include a nasogastric aspirate with red blood, tachycardia and haemoglobin level below 80 g/l[15]. A clear or bilious nasogastric lavage should not be relied on to eliminate high-risk lesions given their association in up to 15 per cent[30].

Various risk-scoring models for UGIB exist. The widely validated Glasgow Blatchford score (range 0–23) uses pre-endoscopic parameters to predict the need for subsequent interventions (blood transfusion, endoscopy or surgery), rebleeding and death[31]. A Blatchford score of 0, found in up to 22 per cent of patients presenting with UGIB, is useful in identifying those who do not require urgent intervention, with a negative LR of 0·02 (95 per cent c.i. 0 to 0·05)[15]. Thresholds of 0 to 3 have been used to identify patients who may be managed safely as outpatients[32,33]. The Rockall score (range 0–11) incorporates both pre-endoscopic and endoscopic findings to predict death, with scores of 2 or less considered to indicate low risk (*Table 2*)[34]. The Blatchford score outperforms the Rockall score in estimating the need for interventions and mortality, and both are superior to the pre-endoscopic Rockall score[35]. In clinical practice, the Blatchford score may be employed increasingly among primary care physicians in the initial assessment of a patient with UGIB, whereas surgeons, who are involved at a later stage, often after the initial endoscopy, may find the Rockall score more relevant. Other scores, such as the modified Blatchford, AIMS65, Acute Physiology And Chronic Health Evaluation II, Baylor, Cedar Sinai and Progetto Nazionale Emorragie Digestive (PNED), require further validation.

Pre-endoscopic proton pump inhibitor

The administration of a high dose of intravenous proton pump inhibitor (PPI), using an 80-mg bolus followed by an 8-mg/h infusion[36], may be considered in patients awaiting endoscopy, although the optimal PPI dose and route have yet to be established. A Cochrane meta-analysis[36] demonstrated that introduction of PPIs before endoscopy diminishes both the incidence of high-risk stigmata of haemorrhage on endoscopy (37·2 *versus* 46·5 per cent; odds ratio (OR) 0·67, 95 per cent c.i. 0·54 to 0·84) and the need for endoscopic haemostasis (8·6 *versus* 11·7 per cent; OR 0·68, 0·50 to 0·93). Mortality, surgery and rebleeding rates were unchanged. Cost-effectiveness analyses have

Table 2 Elements of Rockall risk score

	Score			
	0	1	2	3
Age (years)	< 60	60–79	≥ 80	–
Haemodynamic status				–
Heart rate (beats/min)	< 100	≥ 100		
Systolic BP (mmHg)	≥ 100	≥ 100	< 100	
Co-morbidities	None	–	Ischaemic heart disease, congestive heart failure, or any major co-morbidity	Renal failure, hepatic failure or metastatic malignancy
Endoscopic diagnosis	No lesions and no stigmata of recent haemorrhage or Mallory–Weiss tear	Other	Malignancy of upper gastrointestinal tract	–
Stigmata of recent haemorrhage	No stigmata or pigmented spot	–	Spurting vessel, visible vessel, adherent clot or blood	–

Score modified from Rockall *et al.*[34]. Patients with Rockall scores of 0–2 are considered at low risk of death and rebleeding. BP, blood pressure.

shown that pre-endoscopic intravenous PPIs are more effective and less costly (dominant strategy) than placebo[37], especially if patients with low-risk stigmata are discharged early, and those with high-risk stigmata remain in hospital longer[38]. Although patients with suspected high-risk stigmata and delayed endoscopy might derive incremental benefit from pre-endoscopic PPIs, this pharmacological approach has, at best, a small impact on clinical outcomes, and should not replace appropriate resuscitation and adequate risk stratification, nor delay endoscopy[39].

Prokinetics

Gastric lavage is no longer performed in modern management because of airway safety concerns, coupled with the availability of prokinetic agents administered before endoscopy. Indeed, prokinetics are beneficial in patients at risk of having blood obscuring endoscopic visualization. Erythromycin leads to a decreased need for repeat endoscopy (OR 0·55, 95 per cent c.i. 0·32 to 0·94) in mostly high-risk patients (many requiring admission to the intensive care unit) with active bleeding and/or blood in the stomach (while the evidence for metoclopramide is poor)[40]. Rebleeding, mortality, length of hospital stay and the need for transfusions or surgery were not altered, in contrast to data on variceal bleeding where erythromycin decreased repeat endoscopies, transfusions and length of stay[41].

Endoscopic management

Timing of endoscopy

Endoscopy plays a pivotal role in the diagnosis, risk stratification and treatment of UGIB. Early endoscopy within 24 h of presentation following successful resuscitation is adequate for most patients with UGIB, as opposed to within 12 h for variceal bleeding[42]. Randomized trials looking at early endoscopy (less than 2 to 6 h) showed no improvement in clinical outcomes compared with a delayed approach (less than 24 to 48 h)[43]. A large prospective UK audit[44] demonstrated that endoscopy within 12 h did not affect mortality (OR 0·98, 95 per cent c.i. 0·88 to 1·09) or the need for surgery, compared with endoscopy after 24 h, but led to a decreased length of stay of 1·7 (95 per cent c.i. 1·4 to 2·0) days. Evidence-based consensus guidelines recommend endoscopy within 24 h[23], although more recent recommendations[45,46] have suggested that endoscopy should be carried out within 12 h in acutely ill patients; this shift in recommendations remains supported by limited data[47,48] and is currently controversial[49]. Prompt endoscopy in an otherwise low-risk patient may additionally serve the purpose of identifying those with low-risk stigmata who can safely be discharged from hospital[29].

Endoscopic risk stratification

The endoscopic characterization of stigmata of recent haemorrhage helps to predict prognosis above and beyond bedside parameters, and to guide further endoscopic and medical therapy. Stigmata can be divided into high- and low-risk types using the Forrest classification; high-risk stigmata comprise Forrest Ia (active spurting bleeding), Ib (active oozing bleeding), IIa (non-bleeding visible vessel) and IIb (adherent clot), whereas low-risk stigmata include Forrest IIc (pigmented spot) and III (clean base ulcer). High-risk stigmata are linked to an increased risk of rebleeding. Reported ulcer rebleeding rates without endoscopic haemostasis are as follows: Forrest Ia and Ib, 55 (range 17–100) per cent; IIa, 43 (0–81) per cent; IIb, 22 (14–36) per cent; IIc, 10 (0–13) per cent; and III, 5 (0–10) per cent[50]. The prevalence of stigmata and their

Table 3 Comparison of endoscopic therapies for peptic ulcer rebleeding based on meta-analyses

	Range of odds ratios for rebleeding	Comment
Endoscopic therapy *versus* pharmacotherapy	0·35–0·56[57]	Statistical significance in favour of endoscopy
Thermal + injection *versus* injection	0·36–0·41[58–60]	Statistical significance in favour of thermal + injection therapy
Clips + injection *versus* injection	0·33–0·47[57–61]	Statistical significance in favour of use of clips + injection
Injection + injection *versus* injection	0·60–0·66[58–60]	Statistical significance in favour of use of injection + injection
Dual (injection + second agent) *versus* injection	0·27–0·59[57–60,62]	Statistical significance in favour of use of dual approach
Combination *versus* thermal	0·35–0·79[57–59,62]*	No significance demonstrated for combination therapy
Combination *versus* mechanical monotherapy	0·92–1·22[57,59,62]	No significance demonstrated for combination therapy
Clips *versus* thermal	0·24–0·65[57,61]†	No significant difference found

Thermal, use of electrocautery methods; injection, insertion of adrenaline (epinephrine) or other substances; mechanical, placement of clips; combination, concomitant use of different methods (such as use of injections before clip placement). *Not statistically significant in one of three trials; †not statistically significant in one of two trials.

associated rebleeding rates following endoscopic treatment vary in the literature, probably owing to high inter-observer variability[51,52], and the older pharmacological and endoscopic approaches exhibiting lesser efficacy. Large gastrointestinal haemorrhage registries describe findings of active bleeding (Forrest Ia and Ib) in 2·9–27 per cent of lesions at endoscopy, non-bleeding visible vessels in 6·1–20·2 per cent, adherent clots in 6·5–14·4 per cent, pigmented spots in 1·7–23 per cent and clean base ulcers in 22·3–52·6 per cent[7,8,11,12,53–55]. Observed rebleeding rates after endoscopic therapy range from 19·6 to 42·6 per cent (Forrest Ia and Ib), 19·5 to 38·7 per cent (Forrest IIa), 17 to 32 per cent (Forrest IIb), 9·7 to 15 per cent (Forrest IIc) and 1·1 to 5·1 per cent (Forrest III)[53–55], with discrepancies attributable to heterogeneous patient populations and varying methods of haemostasis.

Endoscopic haemostasis

All patients exhibiting high-risk stigmata should undergo endoscopic haemostasis, in contrast to those with low-risk stigmata who have low rebleeding rates without therapy[23]. Endoscopic haemostasis significantly decreases rebleeding, surgery and mortality rates in patients with active bleeding and non-bleeding visible vessels, but not in those with an adherent clot or a pigmented spot[56]. Endoscopic haemostasis can be achieved using injection, thermal and mechanical modalities; examples of commonly employed methods are described in *Table S1* (supporting information).

Although any endoscopic therapy is superior to pharmacotherapy[57,58], meta-analyses in peptic ulcer bleeding have demonstrated the inferiority of adrenaline (epinephrine) injection as a monotherapy in patients with high-risk stigmata[57–62]. If used, it should therefore be done either before thermal therapy or (usually) following clip application. Beyond this, there is insufficient evidence to recommend further the use of one haemostatic method over another, either alone or in combination (*Table 3*)[57–62].

Adherent clot

Clots should be irrigated to expose the underlying stigmata of recent haemorrhage, which needs to be treated accordingly[23]. Vigorous washing for up to 5 min will dislodge clots in up to 43 per cent of patients[63]. Clots that do not dislodge after aggressive irrigation are considered adherent. Two randomized clinical trials[64,65], which used adrenaline injection and cold guillotining to expose the underlying stigmata, followed by endoscopic haemostasis, demonstrated less rebleeding with endoscopic therapy compared with medical therapy. However, a trial[66] employing high-dose intravenous PPI showed similar rebleeding rates with or without endoscopic therapy in patients with adherent clots, suggesting that either management approach is acceptable, keeping in mind the small numbers of patients on which this recommendation is based[23,58].

Management after endoscopy

There is strong evidence that high-dose intravenous PPI (80-mg bolus followed by 8-mg/h infusion) after endoscopic haemostasis decreases rates of rebleeding (OR 0·49, 95 per cent c.i. 0·37 to 0·65), need for repeat endoscopic therapy (OR 0·32, 0·20 to 0·51) and surgery (OR 0·61, 0·48 to 0·78)[67]. A mortality benefit (OR 0·53, 0·31 to 0·91) was detected in patients with active bleeding and non-bleeding visible vessels treated with PPIs after successful endoscopic haemostasis[67]. Intravenous therapy should be maintained for the first 72 h as most rebleeding occurs during this time[29]. Low-dose and oral PPI cannot

be recommended based on available data[68]. Once-daily oral PPI is generally adequate after completion of the intravenous course, but depends on the aetiology of bleeding, as does the duration[23].

Second-look endoscopy

A preplanned repeat 'second-look' endoscopy 16–24 h after endoscopic treatment is discouraged as part of routine practice. A second look can be considered in selected patients at an especially high risk of rebleeding[23], such as those presenting with haemodynamic instability and a low haemoglobin level, as well as patients whose endoscopy shows active bleeding, large ulcers (over 2 cm) or ulcers in locations suggesting the involvement of large arteries[13]. Indeed, the reported benefits of second-look endoscopy, in terms of rebleeding and surgery, are driven by data antedating the contemporary use of high-dose intravenous PPI, or stemming from very high-risk populations[69].

Acute management and secondary prophylaxis for bleeding

Withholding antithrombotics is often necessary in the setting of acute bleeding, but can carry non-negligible risks. Discontinuation of low-dose aspirin for secondary cardiovascular prevention leads to a significant increase in major adverse cardiac events (OR 3·14, 95 per cent c.i. 1·75 to 5·61) with an interval of 10·7 (95 per cent c.i. 10·25 to 11·07) days before a thrombotic event[70]. The duration of stoppage of antithrombotic agents should be considered carefully.

Patients at high cardiovascular risk benefit from resuming antiplatelet therapy with a PPI as early as possible, after 3–7 days without evidence of rebleeding[23,71]; an Asian placebo-controlled trial[72] showed a decrease in all-cause mortality (1·3 *versus* 12·9 per cent; HR 0·2, 95 per cent c.i. 0·06 to 0·60) when aspirin was reintroduced after adequate haemostasis, at the expense of a non-significant increase in observed rebleeding (10·3 *versus* 5·4 per cent). For patients on dual antiplatelet therapy, such as for drug-eluting stents, attempting to maintain aspirin can delay rates of late stent thrombosis (median time 122 *versus* 7 days) compared with stopping both aspirin and thienopyridine[73,74].

The immediate management of patients on anticoagulants remains poorly characterized and is best managed by a multidisciplinary informed case-by-case approach, balancing cardiovascular risks with that of persistent or rebleeding. The advent of the new haemostatic powders may have a temporizing role to play in this context, especially in light of new oral anticoagulants[27].

With regard to traditional anticoagulation, decreased thrombosis and mortality rates were noted without a significant increase in rebleeding in patients resuming warfarin therapy within 90 days after an episode of gastrointestinal bleeding[75]. Interestingly, case–control studies have, however, failed to demonstrate statistical benefits of PPI in warfarin therapy[76].

In patients who have had ulcer bleeding while taking aspirin, the addition of a PPI after resumption of aspirin decreases the risk of rebleeding[77], and is superior to switching to clopidogrel alone[78,79]. The addition of a PPI to aspirin for secondary cardiovascular prophylaxis appears cost-effective[80]. A similar approach is recommended for clopidogrel users to diminish endoscopic ulcer recurrence[81]. Histamine receptor antagonists are inferior and should not be used for prophylaxis in these settings[82]. Although lesser evidence is available for secondary prophylaxis in patients on dual antiplatelet therapy, with or without anticoagulation, data from PPI use for primary prophylaxis in such individuals may be extrapolated to support their use to prevent recurrent bleeding[82,83].

Diagnosis and management of *Helicobacter pylori* infection

Helicobacter pylori infection should be sought in all patients presenting with an ulcer bleed because *H. pylori* treatment, followed by confirmation of eradication, results in lower rebleeding rates, from 5·6 to 1·6 per cent (OR 0·25, 95 per cent c.i. 0·08 to 0·76) and from 23·7 to 4·5 per cent (OR 0·18, 0·09 to 0·37) in patients with and without long-term antisecretory treatment respectively[84], especially if they require long-term secondary prophylaxis with aspirin[85]. The high false-negative rate for *H. pylori* testing in the acute context of UGIB (0·45 to 0·75) should prompt later repeat testing[23]. The successful treatment of *H. pylori* has been shown to lower the risk of bleeding in this group to the same level as in average-risk patients starting on aspirin[85]. Furthermore, use of antiplatelet agents and non-steroidal anti-inflammatory drugs should be re-evaluated and discontinued when possible after an episode of bleeding, given the high risk of recurrence in this population[86].

Transcatheter arterial embolization

Indications for angiography

TAE has generated interest as an alternative to surgery in high-risk patients with UGIB despite endoscopic treatment[87]. The typical candidate presents with the

following: massive bleeding (transfusion requirement of at least 4 units blood in 24 h) or haemodynamic instability (hypotension with systolic pressure below 100 mmHg and heart rate above 100 beats/min or clinical shock secondary to blood loss); bleeding that has failed to respond to conservative medical therapy, including volume replacement, antacids, H_2 receptor blocking agents or PPIs; and bleeding that has failed to respond to at least one, and sometimes two, attempts at endoscopic control[88]. At that point, low-risk patients are offered the option of surgical intervention, whereas high-risk individuals are directed toward percutaneous embolotherapy. Finally, endovascular treatment can be used after open intervention has failed and bleeding recurs[89].

Types of procedure

In the setting of UGIB, the source of haemorrhage is usually identified by endoscopy. Therefore, angiography is most often performed only as a precursor to transcatheter embolotherapy based on the known vascular supply to the area of abnormality. Angiography in the setting of UGIB is positive for extravasation or abnormal mucosal blush in up to 61 per cent of patients[90,91]. This limited sensitivity for acute bleeding is not problematic, as it is generally believed that empirical embolization of a targeted vascular bed is safe and effective, thus decreasing the prerequisite for positive angiography[91]. Transcatheter intervention to control UGIB takes two forms: the infusion of a vasoconstricting medication (vasopressin), and the mechanical occlusion (TAE) of the arterial supply responsible for the haemorrhage. Vasopressin infusion has lost favour for two main reasons: catheterization can require several days and, more importantly, the emergence of embolization[92].

TAE is an effective means of interrupting blood flow to the bleeding source, while maintaining bowel viability. Although there is a risk of bowel ischaemia and/or infarction, the co-axial catheter systems and the variety of available embolic agents now used for embolization allow very selective and precise treatment, and have decreased the incidence of these complications[87,91,92]. Additionally, the gastrointestinal tract has a rich collateral blood supply, with extensive vascular arcades that permit safe embolization if certain principles are observed. Indeed, using this miniaturized technology, superselective embolization can be performed safely, with a high technical success rate and a low rate of ischaemic intestinal complications[91].

Many published studies have confirmed the feasibility of this approach and reported high technical and clinical success rates, ranging from 69 to 100 per cent and 63 to 97 per cent respectively[90,93,94]. Case series reporting the efficacy of TAE usually comprise patients with a high operative risk, with previous failed endoscopic therapy or with recurrent bleeding after surgery. The abundant collateral circulation in the duodenum explains rebleeding after embolization of the gastroduodenal artery. Indeed, of 16 rebleeding events in a series[90] of 60 patients, 15 occurred after embolization of the gastroduodenal artery and its branches. Complete embolization of the gastroduodenal artery, which includes proximal and distal embolization and exclusion of its two side branches, should be the angiographic endpoint in the event of bleeding from the gastroduodenal artery. Selective superior mesenteric arteriography should be carried out after TAE to ensure that no collateral supply to the bleeding site is present.

Major and minor embolization-related complications developed in 9 per cent of patients in a review[87] of published series of angiographic embolization for acute NVUGIB that included more than 20 patients during a 17-year interval. Access-site complications, dissection of the target vessel, and liver and spleen infarction were the main reported complications in early series[87,95]. Although the risk of significant ischaemia after embolization is known to increase in patients who have had surgery within the same area previously, acute ischaemic complication requiring surgery has rarely been reported in recent series owing to the rich collaterality and use of contemporary techniques[89,91,93,94]. The most significant long-term complication was duodenal stenosis in one series[95], particularly after glue embolization of terminal muscular branches of the gastroduodenal artery (25 per cent). In most series, patients in whom embolization failed or who experienced rebleeding after TAE were treated with repeat endoscopy, repeat embolization or surgery.

Predictors of outcome

Coagulation disorders, a longer time from shock onset to angiography, a larger number of red blood cell units transfused before angiography, and having two or more co-morbid conditions have been shown adversely to affect the success rate of TAE in the largest series assessing prognostic factors[90]. Consequently, when TAE is used, every effort should be made to perform the procedure early after the onset of bleeding, before multiple organ failure occurs, and to correct coagulation disorders before, during and after intervention[87,90,96].

After embolization in patients too sick to undergo open intervention, the mortality rate of patients with UGIB varies between 5 and 40 per cent[87]. A strong correlation has been noted between coagulopathy, clinical failure and mortality after embolization; patients with an impaired coagulation profile are three times more likely to

experience rebleeding after initially successful embolization and ten times more likely to die as a result of bleeding than those with normal coagulation status[87,97]. In other series[97–99], underlying medical problems, such as cirrhosis and malignancy, had a major impact on the mortality rate.

In patients with normal angiographic findings, several studies[100–102] have suggested empirical embolization of the vessel supplying the segment of the upper gastrointestinal tract most likely responsible for the bleeding, based on endoscopic findings. This approach has been found to be effective in achieving bleeding control. Although this technique remains controversial, there is now enough evidence to advocate the practice of endoscopy-directed empirical embolization for angiographically negative UGIB[90,101,102]. The endoscopist can also mark the bleeding sites with clips placed at the junction of the ulcer and the adjacent normal mucosa, to help guide superselective angiography and endovascular treatment, thus increasing the efficacy of the procedure[103].

More controversial is the influence of the type of embolic agent on the clinical outcome. The choice of embolic agent is still debatable. In most series, this choice was at the discretion of the interventional radiologist, according to personal experience, availability, angiographic findings, and capability to perform superselective catheterization of the bleeding vessel. However, several authors[95] have reported a high rate of bleeding recurrence when Gelfoam® (Pfizer, New York, USA) was used alone, whereas the clinical success rate was relatively high in recent series[104,105] in which glue was used as the only embolic agent. Indeed, the use of glue is beneficial in haemodynamically unstable patients because it provides faster and better haemostasis than other embolic agents, without any more complications[104,105]. However, the use of *N*-butyl cyanoacrylate glue requires considerable experience, given the risk of gastric infarction and glue reflux into other vessels. Two studies[90,97] demonstrated a statistically significant association between the use of coils as the only embolic agent and greater rebleeding rates, suggesting that coils should be combined with Gelfoam® or glue using the 'sandwich technique' (*Fig. 1*) in areas with rich collaterals such as the gastroduodenal artery territory.

Role of emergency surgery for acute ulcer bleeding

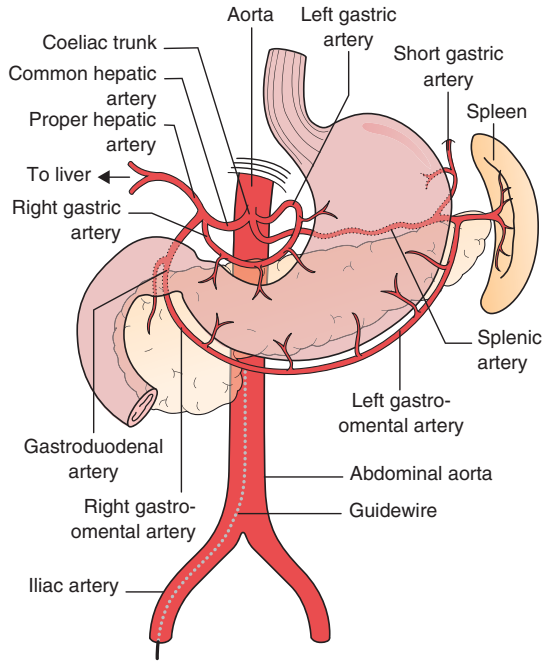
The first UK national audit[6] performed in 1993–1994 revealed an operative rate of 12 per cent among 2071 patients with bleeding peptic ulcers and an associated mortality rate of 24 per cent. In the subsequent audit in 2007[3,106], surgery was carried out in 2 per cent of patients with acute UGIB, with a mortality rate of 29 per cent. The use of surgery has continued to decline, but nonetheless surgery has an important gate-keeping role. The risk of death after surgery is high for several reasons. Patients are often elderly, with significant co-morbid illnesses, and are unable to withstand surgery after major blood loss and hypotension; in addition, endoscopic therapy selects a subgroup of high-risk ulcers for surgery. These ulcers are typically large chronic lesions that represent technical challenges for surgeons.

Timing of surgery

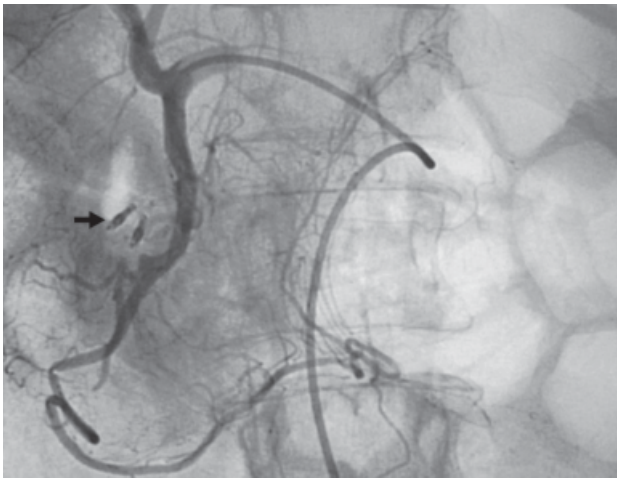
Before the modern era of endoscopic and PPI therapies, the timing of surgery for patients with significant ulcer bleeding was a subject of intense debate. Morris and colleagues[107] published the only randomized trial, which compared early with delayed surgery in 140 patients with bleeding ulcers. The trial showed that, in patients aged over 60 years, early surgery led to fewer deaths (3 of 48 *versus* 7 of 52; $P = 0{\cdot}32$). A significant difference was seen in the subgroup with bleeding gastric ulcers (0 of 19 *versus* 5 of 21; $P = 0{\cdot}01$) treated by early surgery and on analysis by treatment received. The findings of the trial would not be applicable to contemporary practice. Nowadays, surgery is reserved principally for those in whom endoscopic treatment fails. The usual scenarios are massive bleeding uncontrolled by endoscopy, and further bleeding after several endoscopic attempts. The optimal effective number of endoscopic attempts before surgery should be performed has yet to be defined. In a clinical trial[108] that compared surgery with one further endoscopic treatment in patients with rebleeding after initial endoscopic control, further endoscopic treatment was successful in securing haemostasis and avoided surgery in three-quarters of patients. Overall, there were fewer complications in the endoscopic group. In this trial, the rate of gastrectomy in those assigned to surgery was 50 per cent, contrasting with the modern surgical practice of oversewing alone. In a logistic regression model, ulcers larger than 2 cm and hypotension were two factors that predicted failure of further endoscopic treatment[108].

Types of surgery

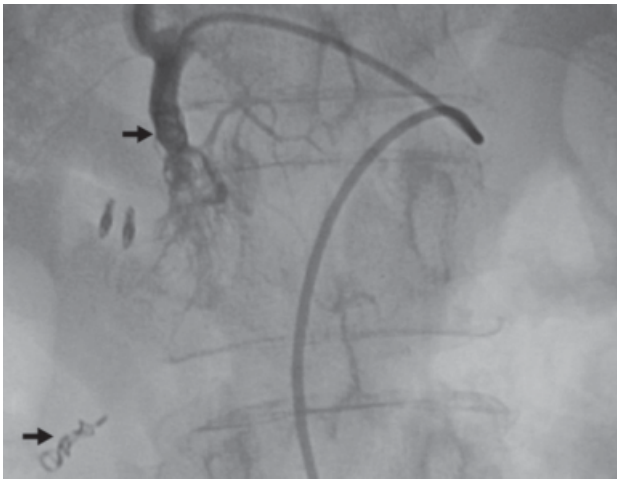
The type of emergency operation for ulcer bleeding is also controversial. Most contend that oversewing alone is adequate as *H. pylori* eradication and/or long-term PPI secondary prophylaxis often cure or prevent recurrence of the disease. In the second national UK audit[3], gastrectomy was used in only 9 per cent of patients who underwent surgery. Based on US national hospitalization records[109], the rates of gastrectomy and vagotomy have fallen from 4·4



a Vascular supply to stomach



b Angiography before embolization



c Coil embolization

Fig. 1 Typical 'sandwich embolization' in a patient with bleeding from a postbulbar duodenal ulcer at endoscopy. **a** Anatomical landmarks and vascular supply to the stomach. **b** Angiography before embolization, guided by clip position (arrow); there is no evidence of active bleeding. **c** Coil embolization of the distal and proximal gastroduodenal artery (with gelatin sponge in the arterial trunk), including the anterior and posterior superior pancreaticoduodenal arteries and the right gastroepiploic artery, to prevent retrograde flow (arrows). The bleeding stopped and no ischaemic complications were reported.

to 2·1 per cent and from 5·7 to 1·7 per cent respectively, in those admitted with complicated peptic ulcer disease between 1993 and 2006. Two randomized trials[110,111] comparing minimal with definitive surgery have been published. A multicentre study[110] in the UK compared minimal surgery (oversewing the vessel, or ulcer excision alone plus intravenous H_2 receptor antagonist therapy) with definitive ulcer surgery (vagotomy and pyloroplasty or partial gastrectomy) in patients with bleeding gastric or duodenal ulceration. The trial was ended prematurely because of high rates of fatal rebleeding in patients who underwent minimal surgery. In the group of 64 patients who received oversewing alone, seven had rebleeding and six of these died. Of the 67 patients who had conventional ulcer surgery, four experienced rebleeding after oversewing and vagotomy but none died. The overall mortality rate did not differ statistically in the two groups: 26 (95 per cent c.i. 14·9 to 36·7) per cent after minimal surgery and 19 (9·9 to 28·9) per cent after conventional surgery.

The French Association for Surgical Research[111] conducted a multicentre trial in patients with bulbar duodenal ulcers, who were randomized to oversewing plus vagotomy and drainage or partial gastrectomy. After oversewing and vagotomy, recurrent bleeding occurred in ten (17 per cent) of 60 patients, six of whom required conversion to a Billroth II gastrectomy. Five of these six patients experienced duodenal stump dehiscence. Among the group of 60 assigned to partial gastrectomy, bleeding recurred in only two patients (3 per cent), both of whom recovered after conservative treatment. Of the 60 patients assigned to partial gastrectomy, Billroth I reconstruction was performed in 18, Billroth I reconstruction plus

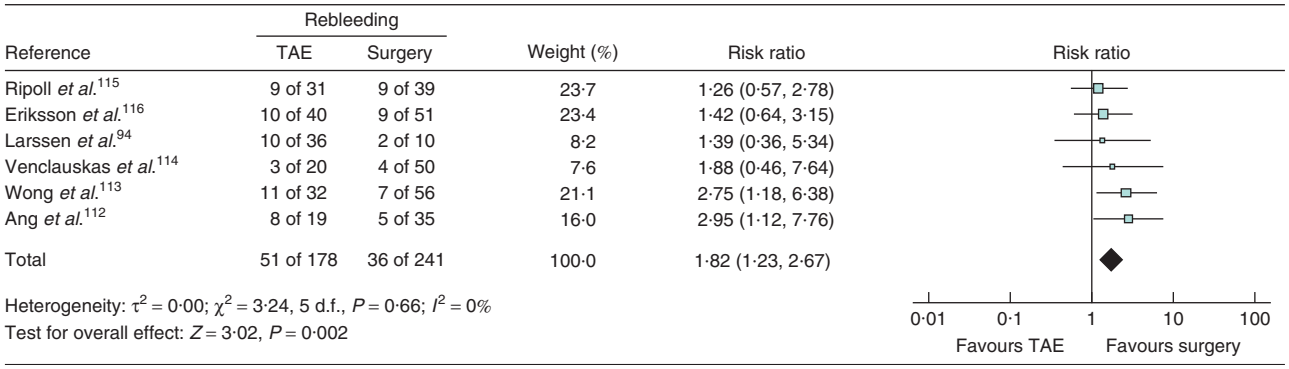


Fig. 2 Risk of rebleeding based on pooled analysis of studies that compared transarterial angiographic embolization (TAE) with surgery in patients in whom endoscopic treatment failed. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

vagotomy in six, Billroth II reconstruction in 20 and Billroth II reconstruction plus vagotomy in 16 patients. No duodenal leak occurred in 24 patients after Billroth I reconstruction, whereas eight (22 per cent) of the 36 patients who received Billroth II reconstruction developed duodenal stump leaks. The rate of duodenal stump leak in the overall gastrectomy group was therefore 13 per cent (8 of 60). On intention-to-treat analysis, the duodenal leak rates were similar in the vagotomy and gastrectomy groups (7 of 58 *versus* 8 of 60 respectively). The study suggests that a Billroth I reconstruction is advised over a Pólya-type reconstruction. After an antrectomy, the stomach remnant should be advanced over the distal edge of the ulcer and a gastroduodenostomy fashioned. The two randomized studies emphasize that oversewing even with vagotomy is associated with a higher rate of recurrent bleeding. Many surgeons with experience in dealing with these 'difficult' ulcers argue for proper ligation of the gastroduodenal artery complex and the use of gastrectomy[111].

Comparison of modalities and collaborative approaches

Transarterial angiographic embolization *versus* surgery

There have been six retrospective comparisons[94,112–116] between TAE and surgery. In pooled analysis, TAE was associated with an increased rate of recurrent bleeding (28·6 *versus* 14·9 per cent; $P = 0·002$) (*Fig. 2*). Patients treated by angiography were older (mean age 74·8 *versus* 67·8 years). The mortality rate was high in both groups but was not significantly different (18·7 per cent *versus* 23·7 per cent; $P = 0·49$) (*Fig. 3*). There is currently an ongoing multicentre randomized trial comparing the two treatment approaches in patients with uncontrolled bleeding by endoscopic methods (registration number NCT00766961).

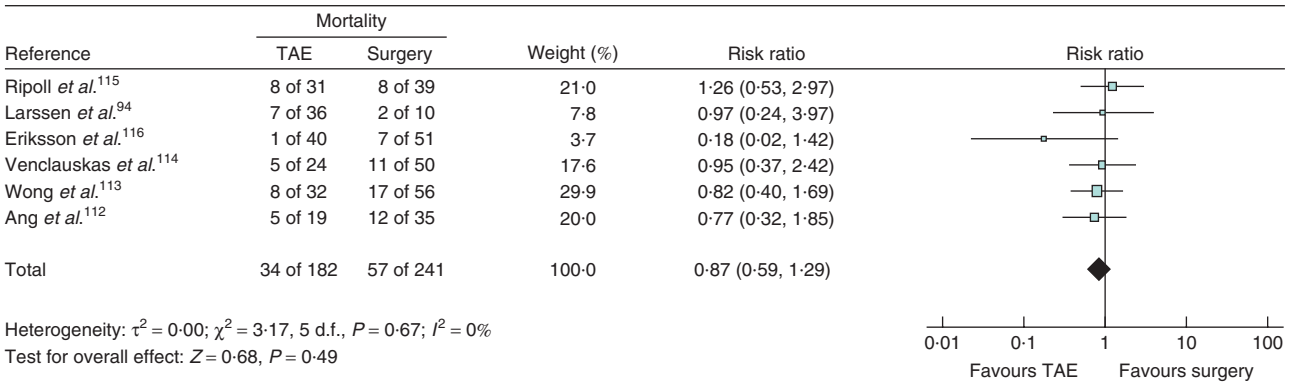


Fig. 3 Mortality based on pooled analysis of studies that compared transarterial angiographic embolization (TAE) with surgery in patients in whom endoscopic treatment failed. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

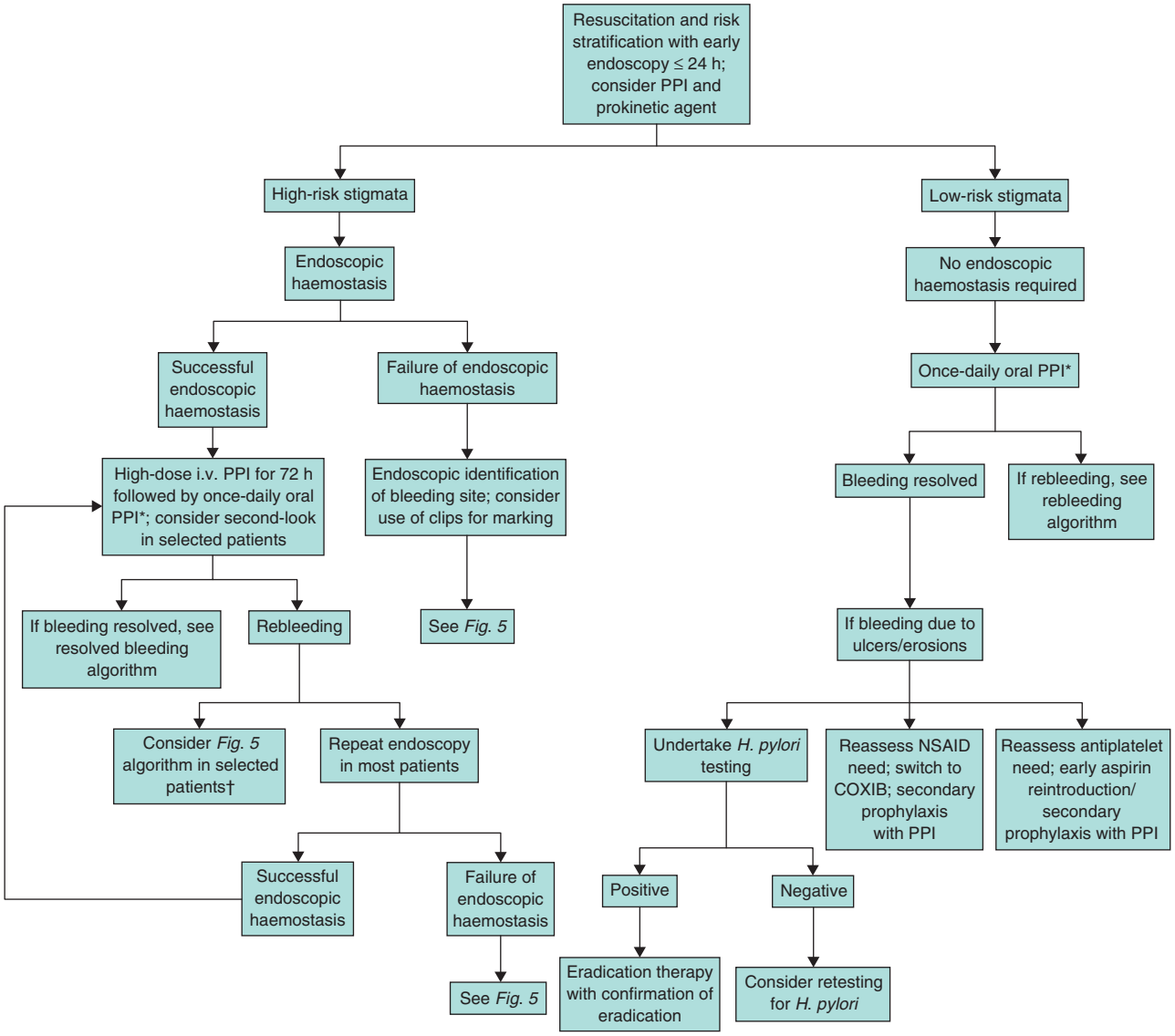


Fig. 4 Algorithm for the initial management of upper gastrointestinal bleeding. Patients with non-variceal upper gastrointestinal bleeding should undergo prompt resuscitation followed by early endoscopy within 24 h to identify the severity of the stigmata of recent bleeding. Patients with high-risk stigmata should undergo endoscopic therapy. In the event of rebleeding, a second attempt at endoscopic haemostasis should be made. Transcatheter arterial embolization and surgery may be considered in selected patients. Appropriate secondary prophylaxis needs to be offered to diminish the risk of recurrent bleeding. *Proton pump inhibitor (PPI) dose dictated by endoscopic findings as patients with some conditions (such as oesophagitis) require a higher dose. †May consider in patients with very severe bleeding or previous rebleeding. NSAID, non-steroidal anti-inflammatory drug; COXIB, cyclo-oxygenase 2 inhibitor; *H. pylori*, *Helicobacter pylori*

Prophylactic transarterial angiographic embolization

A more recent approach has been to pre-empt recurrent bleeding by selecting patients at high risk of continued or recurrent bleeding after endoscopic haemostasis for TAE. Endoscopists leave haemoclips at the bleeding point for its easy identification during angiographic embolization, regardless of active extravasation at the time. The key to the success of this strategy is the accurate identification of those at such a risk, so that this approach and its risks are justified. Large ulcers in the duodenal bulb or at the angular notch or lesser curvature of the stomach have consistently been identified as those most likely to

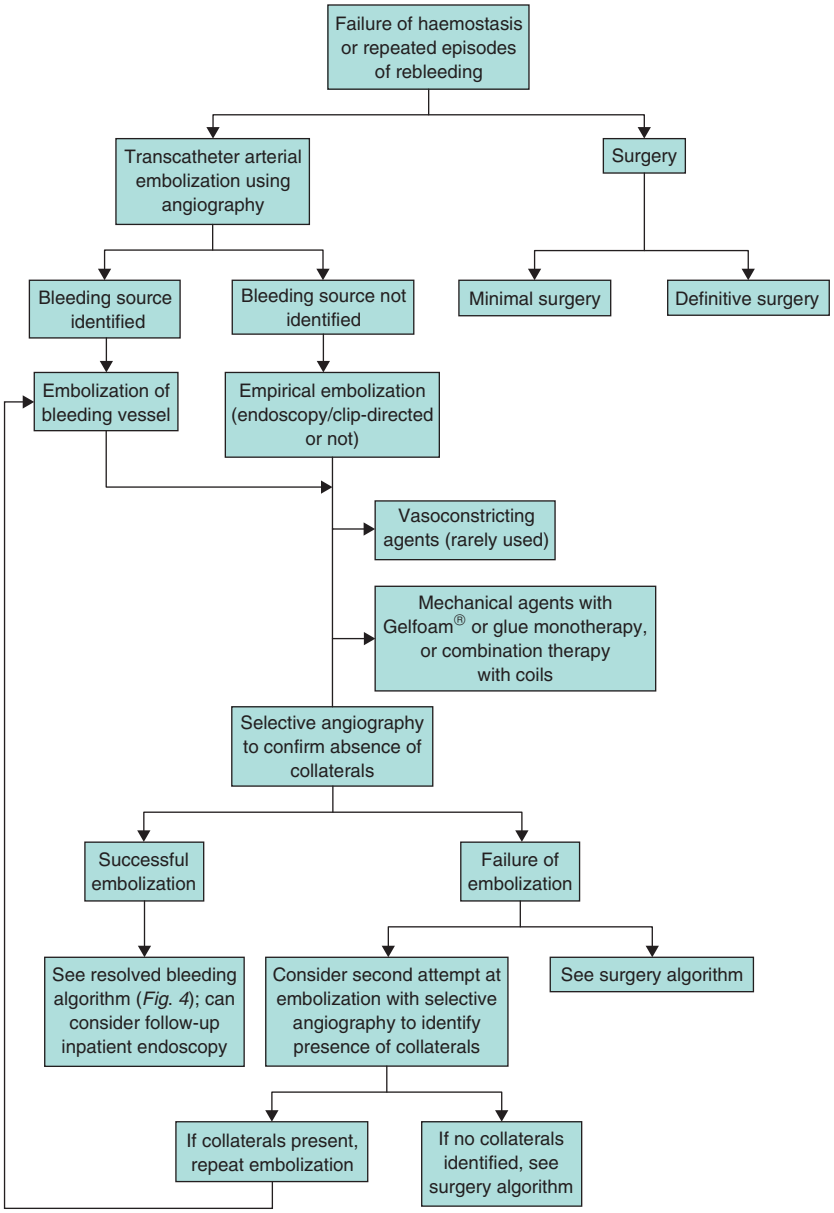


Fig. 5 Algorithm for the management of recurrent bleeding. Transcatheter arterial embolization and surgery can both be considered in patients in whom immediate endoscopic haemostasis has failed, or who experience recurrent episodes of rebleeding despite repeat endoscopic therapy. The decision to pursue one modality over another depends on patient characteristics, physician preference and local availability

fail endoscopic treatment[117]. Such ulcers often involve the full thickness of gastroduodenal walls and erode into major subserosal arterial complexes of either the gastroduodenal or left gastric artery. In addition, patients with such ulcers are often old, have significant co-morbid illnesses and present in shock with major bleeding. They tolerate blood loss poorly and often lapse into organ failure after major bleeds. Two unpublished randomized trials are currently investigating the role of prophylactic TAE in forestalling rebleeding from high-risk ulcers (NCT01125852 and NCT01142180); preliminary, possibly underpowered, data suggest a non-significant trend towards decreased rebleeding using this more aggressive approach[118].

Conclusion

The prevalence, management and indeed prognosis of patients with UGIB have evolved significantly over the past decade, with improved diagnostic and therapeutic options, including pharmacological, endoscopic, radiological and surgical approaches complementing each other according to the clinical situation. A collaborative approach integrating endoscopic, radiological and surgical expertise is crucial for further improving outcomes, especially in high-risk patients (*Figs 4* and *5*).

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Selection of commonly employed methods for endoscopic haemostasis (Word document)