

Management of Non-Variceal Upper Gastrointestinal Bleeding – Where are we in 2017?

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Introduction:

Upper Gastrointestinal bleeding (UGIB) is one of the most common acute GI emergencies. The associated mortality has remained unchanged for the past two decades, being higher among elderly patients with co-morbidities [1] [2]. In the UK, GI bleeding is one of the commonest medical emergencies with approximately 85,000 cases per year with 4000 deaths annually [2].

The majority of upper GI bleeds (80-90 %) are non-variceal. Patients often present with symptoms such as haematemesis, coffee-ground vomit, drop in haemoglobin, melaena and haematochezia, with or without haemodynamic instability [3]. The presence of pre-existing co-morbidities is a significant contributor to mortality in elderly patients with UGIB [4]. Common aetiologies include: Peptic Ulcer Disease, Oesophagitis, Gastritis, Mallory-Weiss Tear, Dieulafoy Lesion, Gastroesophageal Varices, Cancer, and Haemobilia [5][6][7][8][9].

Despite advancements in therapeutic and interventional endoscopy, acute UGIB (AUGIB) remains a challenge for clinicians and endoscopists worldwide. The clinical community acknowledge that the management of these patients requires streamlining and improvement.

What is the problem?

The majority of the Non-Variceal Upper Gastrointestinal Bleed (NVUGIB) in the UK are caused by peptic ulcer disease. UGIB has an enormous burden on health care. In-patient bed stay, endoscopy provision and blood product transfusions are the main contributors to the overall cost of UGIB. The annual initial in-hospital treatment cost for all AUGIB cases in the UK was estimated to be £155.5 million with over £93 million (60%) of this cost due to in-hospital length of stay, £38.5 million (25%) to endoscopy and £12.6 million (8%) to blood transfusion [10].

UGIB have an associated mortality rate of 10% [1] [11] and endoscopic therapy remains the gold standard treatment. Early endoscopy (within 24 hours) is recommended for most patients with AUGIB, in order to achieve prompt diagnosis, provides risk stratification and haemostasis [12]. The UK's National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2015 concluded that only 44% of patients presenting with AUGIB received good care overall [1].

The Significance of Co-morbidities:

Mortality in AUGIB is rarely related to the actual haemorrhage, but rather to co-existing co-morbidities. Recent studies have shown that about 18% of the total mortality is directly related to GI haemorrhage with the majority of deaths caused by concurrent co-morbidities.

Pulmonary disease (24%), multi-organ failure (24%), and terminal malignancy (34%) are the most common co-morbidities [13].

Blood Product Transfusion before endoscopy:

The United Kingdom Comparative Audit (2007) of UGIB and the Use of Blood has shown that AUGIB is a significant consumer of blood products in the UK. The study included 6750 patients from 208 hospitals across the UK, with 43% of patients needing at least one unit of blood transfusion [14]. GI bleeding is the second commonest medical reason for transfusion in the UK after haematological malignancy, accounting for 14% of all blood transfusions [14]. 15% of GI bleed patients receive 4 or more units of blood during their inpatient stay. Blood product use is inappropriate in 20% of cases [15].

Current evidence has shown favourable outcomes in patient's whose Hb transfusion commenced once haemoglobin (Hb) dropped below 70g/L [16]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends a restrictive blood transfusion strategy that aims for a target Hb between 70g/L and 90g/L. A higher target Hb should be considered in patients with significant co-morbidity (e. g. ischemic cardiovascular disease) [17]. In addition at the time of discharge, a restrictive target of Hb 80-100 g/L has shown to have better outcomes in those presenting with AUGIB [18].

New Anti-Coagulant drugs:

The emergence of the direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban and edoxaban) has reduced regular serum monitoring that is required for patients on warfarin; however there is a 25-30% increased risk of GI bleeding with the use of DOAC when compared with warfarin [19] [20]. The risk is mostly relevant in the elderly and those with hepatic disease, renal disease and patients on concomitant antiplatelet agents. In the case of an AUGIB, reversal agents can be used; however different assays are needed to indirectly quantify DOAC level prior to reversal. These assays include the dilute Thrombin Time (TT) and Ecarin clotting time (ECT) for dabigatran and the drug-specific calibrated anti-Xa factor assay for rivaroxaban, edoxaban and apixaban [21]. Reversal agents exist (prothrombin complex concentrate (PCC), activated PCC, Idaricizumab) with many others currently on clinical trials [20].

What are the commonly used risk stratification tools?

Early patient risk stratification will allow the planning and timing of life saving procedures such as endoscopic therapy with adequate and safe triage. The primary aim of the initial assessment is to determine whether endoscopy is required urgently or it can be delayed or even managed in the outpatient setting [2]. At present 3 such scores exist and are in clinical practise.

Glasgow-Blatchford Score (GBS):

The Glasgow-Blatchford Score (GBS) utilises both clinical (Pulse, systolic BP, presence of melaena, presentation with syncope, presence of hepatic disease and heart failure) and serological parameters (Urea, Hb), that are easily available at initial assessment which allows the clinician to identify patients that would be suitable for management in the outpatient setting [22]. The ESGE and NICE recommend the use of the GBS for pre-endoscopy

risk stratification. Patients with the score of 0 or 1 do not require hospital admission and can be safely discharged and managed with outpatient endoscopy [17] [23].

Table 1: Glasgow Blatchford Score (GBS):

Glasgow Blatchford Score (GBS) for Gastrointestinal bleeding:	
Blood urea (mmol/L)	Score value
6.5–7.9	2
8.0–9.9	3
10.0–25.0	4
>25.0	6
Haemoglobin for men (g/L)	
120–129	1
100–119	3
<100	6
Haemoglobin for women (g/L)	
100–119	1
<100	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse \geq 100/min	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease*	2
Cardiac failure†	2
*Known history, or clinical and laboratory evidence, of chronic or acute hepatic disease	
†Known history, or clinical and echocardiographic evidence, of cardiac failure	

Rockall score (RS):

In contrast, the Rockall score (RS) combines clinical parameters with endoscopic findings in order to predict the risk of mortality. Lack of endoscopic findings in the initial assessment of a patient with AUGIB may deter the clinician from using the RS; however full post endoscopy RS remains an important tool in predicting mortality rate [24].

Table 2: Rockall Score:

Rockall Score for Gastrointestinal bleeding:					
	0	1	2	3	
age	<60	60-79	>80		initial score criteria
shock	no shock	HR > 100	HR > 100, SBP < 100		
co-morbidity			cardiac failure, ischaemic heart disease	renal failure, liver failure, disseminated malignancy	
diagnosis	malory weiss, no lesion, no stigmata of recent haemorrhage	all other diagnoses	malignancy of upper gastrointestinal tract		additional criteria for full score
stigmata of recent haemorrhage	none or dark spot		fresh blood, adherent clot, visible or spirting vessel		
maximum additive score prior to diagnosis = 7					
maximum additive score after diagnosis = 11					

The AIMS65 score:

The AIMS65 score is designed to predict in-hospital mortality, length of stay, and cost of GI bleeding. In comparison to GBS and RS, it is superior in predicting in-patient mortality [25]. AIMS65 score is inferior to GBS and RS in predicting re-bleeding. GBS, RS and AIM 65 are similar in predicting length of hospital stay [25][26]. GBS is more accurate in terms of detecting transfusion need, re-bleeding rate and endoscopic intervention rate [25][27].

Table 3: AIMS 65 Score:

AIMS 65 Score:	
	Score
age > 65	1
systolic BP < 90 mm Hg	1
altered mental status	1

INR > 1.5	1
albumin < 30 g/L	1

Table 4: In-Hospital mortality rate based on AIMS 65 Score:

In-Hospital mortality rate based on AIMS 65 Score:	
Total Score	mortality rate
0	0.30 %
1	1.20 %
2	5.30 %
3	10.30 %
4	16.50 %
5	24.50 %

What is the optimal timing of endoscopy?

The benefit of early endoscopy in the management of NVUGIB remains controversial [12]; however, endoscopy has an important role in obtaining diagnosis with a sensitivity of 90-95% at locating the bleeding site [23].

Several studies have investigated the effect of endoscopy timing on clinical outcomes with varying results. In haemodynamically stable patients with ASA grade 1 or 2, early endoscopy within 12 hours of presentation, has no effect on mortality or recurrent bleeding [28][29][30]; however more high-risk endoscopic lesions are identified [31] in those receiving early endoscopy and these patients tend to have a shorter length of hospital stay. [32] [33] [34] Early endoscopy in haemodynamically stable patients with ASA grade 3 to 5 is associated with lower in hospital mortality. In patients with hemodynamic instability, early endoscopy is associated with lower in-hospital mortality. [32] Although 2–10% of patients with AUGIB can die from their AUGIB, mortality in 80 % of these patients is due to other non-bleeding co-morbidities [35] [13] [23].

What are the common pharmacological therapies?

Proton Pump Inhibitors:

Pharmacological agents such as Proton pump inhibitors (PPI) have significantly reduced the incidence of peptic ulcer disease (PUD) [36]. Pre-endoscopic use of PPI reduces the detection rate of high-risk stigmata during endoscopy and the need for endoscopic therapy [2]; however, there is no significant impact on the amount of blood transfusion, rebleeding rate, surgery, or death within 30 days [23][37].

Prokinetic Drugs:

The administration of prokinetic drugs such as metoclopramide and erythromycin has shown to improve endoscopic diagnostic yield in patients with AUGIB and reduced the need for repeat endoscopy [2]. This is useful in cases where the upper GI tract is filled with large volume of blood; however there is lack of evidence in improving the duration of hospitalization, transfusion requirements, or surgery [38].

Tranexamic Acid:

Tranexamic acid, a derivative of the amino acid lysine, has anti-fibrinolytic effect by preventing the degradation of fibrin networks [39]. Studies have shown that it decreases re-bleeding and mortality in AUGIB, without increasing the thromboembolic adverse effects; however, its routine use in clinical practice has not been recommended as further clinical trials are needed [40] [41].


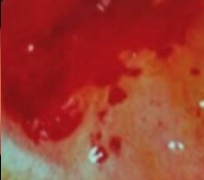

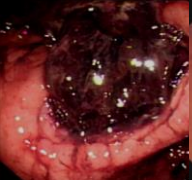

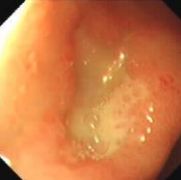
What are the available endoscopic therapeutic modalities?

The endoscopic management of UGIB has evolved in recent decades as therapeutic modalities available to the endoscopist have evolved, driven by innovations in new techniques and accessories. Endoscopy in patients with AUGIB is effective in diagnosing and treating most causes of UGIB [2]. The Forrest Classification categorises the lesion morphology at the time of index endoscopy, allowing the endoscopist to decide when to intervene and prognosticate the risk of re-bleeding [42]. This categorization has also been shown to correlate with the need for surgery and mortality [43]; however, there is significant inter-observer disagreement in categorising the bleeding site, hence accurate photographic documentation is paramount [44].

Table 5: Forrest Classification:

Forrest Classification		
Stage	Characteristics	Re-bleeding
Ia	Spurting Bleed	60 - 100 %
Ib	Oozing Bleed	50%
II		
Ila	Non-Bleeding Visible Vessel	40 - 50 %
Ilb	Adherent Clot	20 - 30 %
Ilc	Flat Spot in ulcer crater	7 - 10 %
III		
III	Clean Base Ulcer	3 -5 %

Diagram 1: Showing different types of bleed based on the Forrest Classification:

Ia	Ib	IIa	IIb	IIc	III
Spurting bleed	Oozing bleed	Non-bleeding visible vessel	Adherent clot	Flat spot in ulcer crater	Clean base ulcer
					

What are the available endoscopic haemostatic techniques?

Several endoscopic treatment modalities have been developed, these include injection methods, heat cauterization, and mechanical therapy.

Adrenaline injection Therapy:

This includes injection of dilute adrenaline (1:10,000) at the site of bleeding. It reduces blood flow by temporarily creating local tamponade and vasoconstriction of blood vessels. Injection of large volume epinephrine (>13 ml) can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcer and is superior to injection of lesser volumes [45] [46] [47].

Thermo-Coagulation:

Thermo-coagulation uses direct contact with the bleeding site with thermal energy delivered via a variety of devices. Heater probe consists of a Teflon coated hollow aluminium cylinder with inner heating coil. It utilizes electrical current to generate heat. It The Gold Probe has a rounded gold distal tip with good conductivity and has irrigation and injection capability, in addition to delivering heat for thermo-coagulation [48].

Argon Plasma coagulation (APC) is a non-contact ablative modality that uses steam of ionized gas to conduct electricity for the coagulation of bleeding tissue [49].

Mechanical Therapy – Clips:

Mechanical therapy is an attractive method for achieving endoscopic haemostasis. It has a significant impact on achieving haemostasis in difficult and challenging cases and a significant impact on outcomes [50].

Mechanical therapy with endoscopic clips has been shown to be effective by physically obstructing the blood flow in the vessel; however, this technique will require direct visualisation of the bleeding point and culprit vessel. Successful application of clip is better in achieving haemostasis when compared to injection therapy alone but similar to thermo-coagulation [51].

The over-the-scope clip (OTSC) has been reported to effectively achieve haemostasis and significantly reduces re-bleeding and re-bleeding associated mortality in NVUGIB. A recent multicentre study was able to show a haemostasis rate of 92.4 % with OTSC as a monotherapy in the treatment of acute NVUGIB with significant reduction in the occurrence of bleeding and mortality of re-bleeding [52].

Dual and triple therapy is better than monotherapy:

Dual endoscopic therapy is superior to monotherapy with adrenaline injection alone in the management of patients with high risk bleeding peptic ulcer; Dual therapy reduces the risk of recurrent bleeding, the risk of emergency surgery [50] and mortality [53].

The possible adverse events from dual therapy include perforation and gastric wall necrosis, with very low occurrence rate. Dual therapy remain to be superior to monotherapy with epinephrine [54] [23].

The Doppler endoscopic probe (DEP):

Doppler probe through the accessory channel of a standard endoscope has been used to assess the blood flow in the superficial blood vessels at the site of bleeding peptic ulcer post endoscopic therapy. The audible signal generated by the probe is able to determine the type of blood flow (arterial or venous) and the location of the bleeding vessel [55][56].

Doppler signal from an ulcer, post endoscopic therapy has been associated with a higher risk of re-bleeding [56] [57]; however, lack of audible signal post endoscopic therapy is not associated with improvement in re-bleeding rate [43].

Is intervention radiology and surgical management suitable for GI bleeding?

Interventional radiology (IR) has shown to provide diagnostic imaging and endovascular therapeutic interventions that can localise the source of bleeding and provide endovascular embolization to achieve haemostasis successfully when conventional endoscopic haemostasis has been unsuccessful. [58] [59] A study by Kramer *et al*, was able to show that IR can control UGIB and achieve haemostasis with the use of minicoils for the embolisation of bleeding vessels with reduced risk of serious complications [60].

Figure 1: Post-short gastric arteries embolization angiographic follow-up [59]



What is the optimum post procedure management?

Post endoscopic treatment with high dose infusion of PPI (bolus of 80 mg followed by 8 mg per hour for 72 hours) in bleeding peptic ulcers, significantly reduces the risk of recurrent bleeding [61]. Re-bleeding rate has also been shown to be associated with the Hb at the time of discharge. The re-bleeding rate in patients with a discharge Hb between 80 and 100 g/L is not significantly different when compared to patients with higher Hb at discharge [18]. In addition, a discharge Hb between 80 and 100 g/L is associated with a lower consumption of Red Blood cells [18].

Re-bleeding is more common in patients with high stigmata lesions at the time of endoscopy, hence repeat endoscopy and treatment should be considered in all high risk bleeds in particular, those with the need to recommence anti-coagulation and patients whom have had limited endoscopic therapy at the initial endoscopy. Surgery should be considered in those not responding to endoscopic therapy or radiological embolisation, taking into account, patient's status and co-morbidities [23].

What are the future developments?

The development of a risk stratification tool relevant to all GI bleeds should be an essential point of focus for all clinicians managing GI bleeding. Several novel modalities have been developed for the investigation and treatment of GI bleeding in recent years. These show promising results in achieving prompt diagnosis and haemostasis.

Video capsule endoscopy:

The use of video capsule endoscopy (VCE) in the emergency department (ED) as a risk stratification tool for identifying high and low risk UGIB patients has been evaluated. It has shown potential to identify high and low-risk patients presenting with signs of AUGIB, helping to determine the need for intervention with significant reduction in the time to emergent endoscopic therapy [62]. VCE in the ED is safe and effective in identifying AUGIB

[63]. A study by Meltzer *et al*, looked into the use of VCE in the ED performed by a gastroenterologist or a VCE trained clinician. The aim was to determine whether patients with signs and symptoms of upper GI bleeding can be discharged with outpatient follow up endoscopy. A total of 25 subjects were enrolled with excellent tolerance to the VCE. The study was able to show a sensitivity of 88 % with a specificity of 64 % for the detection of fresh blood in the upper GI tract [64]. Similar studies have shown significant reduction in hospital admissions with no difference in the clinical outcome in terms of recurrent bleeding and 30-day mortality in the VCE group and those receiving standard treatment [65]. This is very exciting and further studies will be able to provide more data on this unique modality for the diagnosis of patients in the ED. This will potentially have a great impact on the number of hospital admissions [64].

Hemospray:

Hemospray is a novel proprietary mineral blend that forms a mechanical barrier over the bleeding site when applied endoscopically. It gives the endoscopist the opportunity to apply therapy in challenging anatomies. The multi centre European SEAL study [66] and the French GRAPHE study [67] have both shown high haemostasis rates with the use of Hemospray as monotherapy and in combination with conventional methods. These results have been reflected by the current and on-going prospective International Multicentre Hemospray Registry (Alzoubaidi *et al*, UCL, London) showing an overall haemostasis rate of 86%. Expansion of this study is currently in progress and shall provide further evidence on the use of Hemospray as monotherapy, dual therapy and rescue therapy in various pathologies [68].

EndoClot:

The EndoClot (EndoClot Plus Inc., Santa Clara, CA, USA) is a polysaccharide haemostatic powder that can be delivered endoscopically to the site of bleeding in the GI tract without the need for direct mucosal contact. It is composed of absorbable polymer particles, that absorbs water from the blood on the surface of the bleeding site, hence increasing the concentration of platelets and clotting factors, resulting into haemostasis [69][70]. Further clinical trials are awaiting.

Conclusion:

GI bleeding remains to be a challenging clinical emergency with significant mortality and morbidity that remains unchanged these past 2 decades; however, with adequate service planning and adherence to robust guidelines, improved and desirable outcomes can be achieved.

Patients with AUGIB should be admitted to units that provide a 24/7 GI bleed service with anaesthetic support and access to interventional radiology and surgery. Risk stratification and adequate resuscitation prior to any endoscopic therapy is paramount and must supersede the interventional endoscopy as the key initial process in the management of patients with AUGIB.

The timing of endoscopy is dependent on the presenting signs, taking into account the clinical status of the patient. The endoscopic therapy of all acute NVUGIB should not rely on monotherapy alone but a combination of injection therapy with other modalities such as

clips, thermo-coagulation or both. Second look endoscopy is recommended in patients with signs of re-bleeding.

Further developments of new techniques will assist future generations in the management of AUGIB; however, all endoscopists must acquire sufficient training in order to provide the best treatment options. This would require appropriate facilities and training at all hospitals nationwide.

Further studies should focus to explore which treatment modalities are more effective in specific pathologies as currently no single modality is capable of treating all pathologies. Finally, the focus of treatment should not only be the endoscopic therapy and a holistic approach is encouraged in order to optimise treatment by managing multi-organ failure and co-morbidities [13].

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