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Modern-day management of upper gastrointestinal haemorrhage

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SUMMARY

Acute upper gastrointestinal haemorrhage (AUGIH) is a common medical emergency and can present with life threatening haemorrhage. In the UK, there are 70 000 hospital admissions per year. In the majority of cases, the aetiology is non-variceal in origin, but in other cases it is due to variceal bleeding in patients with cirrhosis. It is also a leading indication for transfusion of blood components. This review explores recent randomised data on the efficacy and safety of red blood cell transfusion for AUGIH. In addition, the evidence base for use of other blood components and pro-haemostatic pharmacological agents is discussed, including acid suppression, antifibrinolytics and fibrinogen.

Key words: gastrointestinal haemorrhage, management, red blood cell transfusion.

Acute upper gastrointestinal haemorrhage (AUGIH) is defined by convention as bleeding arising from the oesophagus, stomach or duodenum. It is a common medical emergency and can present with life threatening haemorrhage. The UK incidence is 100–150 per 100 000 adults resulting in 70 000 hospital admissions annually (Crooks *et al.*, 2011) and the burden of morbidity, mortality and cost to the health services is high (Crooks *et al.*, 2011). Despite improvements in the outcome of patients with AUGIH in the past 2 decades, case fatality remains appreciably high even in the most modern of healthcare systems (Campbell *et al.*, 2015), although this is driven largely by concurrent comorbidity rather than death directly due to haemorrhage.

The aetiology of haemorrhage can be broadly considered to be non-variceal or variceal in origin. In the West, non-variceal upper gastrointestinal haemorrhage (NVUGIH) accounts for 85% of presentations, the major causative lesion being peptic ulcer disease, followed by erosive diseases such as oesophagitis, gastritis and duodenitis (Jairath & Barkun, 2012). Risk factors for developing NVUGIH haemorrhage include old age, socio-economic disadvantage, co-morbidities such as chronic renal disease, *Helicobacter pylori* infection and several pharmaceutical agents including non-steroidal anti-inflammatory agents (NSAIDS), aspirin, cyclo-oxygenase (COX) 2 inhibitors and anticoagulants. The remaining presentations (10–15%) are secondary to variceal haemorrhage in patients with liver cirrhosis (Jairath & Barkun, 2012) in whom bleeding can be copious, because of the underlying mechanism of bleeding (portal hypertension) and complex derangements in the coagulation pathways.

Of particular relevance to agencies involved in the supply of blood, AUGIH is one of the largest inductions for red blood cell (RBC) transfusion (Wells *et al.*, 2009). In 2013–2014, 1·7 million units of RBCs were issued in England, with an estimated 200000 U for AUGIH alone. Practice in large cross-sectional surveys has been variable (Jairath *et al.*, 2011; Jairath & Barkun, 2012), and observational data had indicated an association between liberal RBC transfusion and excess mortality (Hearnshaw *et al.*, 2011; Restellini *et al.*, 2013). Two large randomised trials have now been published, which provide the strongest evidence to date to inform RBC transfusion practice for AUGIH (Jairath *et al.*, 2015; Villanueva *et al.*, 2013). This review discusses the broad approach to managing patients with AUGIH, with a focus on the use of blood components for AUGIH, pharmacological agents which target the coagulation cascade and the approach to managing antiplatelet drugs and oral anticoagulants in the face of bleeding.

GENERAL APPROACH TO MANAGING AUGIH

Regardless of whether the source of bleeding is anticipated to be non-variceal or variceal in origin, principles of management are similar. These include prompt assessment and restoration of circulating volume, risk stratification using validated scoring systems (Jairath *et al.*, 2015), administration of pharmacological

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agents prior to endoscopy, timely performance of endoscopy for diagnosis and to administer endoscopic therapy in high-risk lesions, and finally post-endoscopic care.

The initial priority is to asses airway, breathing and circulation, as patients are at risk of haemodynamic shock and airway compromise due to aspiration of blood. All patients with features of shock should be blood-typed and cross-matched, with blood sent for haemoglobin, platelets, coagulation time and electrolytes. As haemodynamic shock is an independent risk-factor for increased mortality (Rockall *et al.*, 1995, 1996) restoring circulating volume takes priority over endoscopy. Randomised trials in other critically ill cohorts found no difference in the efficacy or safety of colloids versus crystalloids (Perel & Roberts, 2011), therefore fluid challenge with either product could be used before blood component transfusion.

SPECIAL CONSIDERATIONS – LIVER DISEASE

The incidence of liver cirrhosis is rising in the UK, with approximately 8000 new cases diagnosed per year (Fleming *et al.*, 2008). Cirrhosis gives rise to the formation of gastro-oesophageal varices, which develop in up to 50% of patients directly as a result of portal hypertension and each episode of acute variceal haemorrhage (AVH) is associated with over 20% mortality. Varices form as a result of portal hypertension and is assessed by hepatic venous pressure gradient (HVPG); HVPG greater than 10, 12 or 20 mm Hg are associated with the primary development of varices, AVH and continued bleeding/rebleeding respectively, which is of particular importance when considering the approach to volume repletion and transfusion volumes following haemorrhage (Moitinho *et al.*, 1999).

The main factors that are thought to contribute to bleeding in cirrhosis include sepsis and uraemia (Jairath *et al.*, 2013). Infection has been associated with increased circulating heparinoids in patients with cirrhosis and active bleeding, which may indirectly interfere with coagulation (Senzolo *et al.*, 2007). Use of prophylactic antibiotics following variceal haemorrhage has been shown both to reduce severity of bleeding and early rebleeding in randomised trials (Jun *et al.*, 2006; Hou *et al.*, 2004). Uraemia, which may be a result of concomitant renal impairment in patients with cirrhosis, may also contribute to a bleeding tendency due to abnormal platelet–vessel wall interactions and platelet dysfunction (Benigni *et al.*, 1993; Escolar *et al.*, 1990). Cirrhosis is also characterised by a complex-acquired coagulopathy characterised by deficiencies in pro- and anti-coagulant factors (Tripodi *et al.*, 2009), anaemia (Thachil, 2011), thrombocytopenia (Pradella *et al.*, 2011), dysfibrinogenaemia (Francis & Armstrong, 1982) as well as hyperfibrinolysis (Ferro *et al.*, 2009). There is the long-standing dogma that patients with cirrhosis are 'auto-anticoagulated', based not only on an abnormal prothrombin time but also the frequent occurrence of bleeding. Although cirrhosis is traditionally considered a pro-haemorrhagic disorder, recent evidence indicates a 'rebalanced haemostasis' such that clot formation is normal, provided platelet counts are $>50 \times 10^9\ L^{-1}$. Whilst platelet levels are reduced in cirrhosis, there is some evidence that platelet hyperactivation may compensate for due elevated levels of the platelet adhesion protein von Willebrand factor and reduced levels of its cleaving protease ADAMTS13 (Mannucci *et al.*, 2001). Finally, anaemia and excessive fibrinolysis may also contribute towards bleeding.

RBC TRANSFUSION FOR AUGIH

The purpose of RBC transfusion after haemorrhage is to restore global and regional oxygenation. The benefit of this is unquestionable in severe haemorrhage, but in patients with less severe haemorrhage the evidence base to inform transfusion thresholds has been less clear. Randomised trials in other therapeutic areas such as critical care (Hebert *et al.*, 1999) and hip surgery (Carson *et al.*, 2011) have shown that a restrictive approach to RBC transfusion using thresholds of $70–80\ g\,L^{-1}$ results in fewer transfusions compared with a higher transfusion thresholds, without any apparent harm. It has been unclear whether these findings can be extrapolated to patients with AUGIH where there is rapid development of anaemia and acute haemodynamic compromise, usually in the context of advanced age and co-morbidity. A Cochrane review of RCTs in 2010 found only three small, historical trials comparing transfusion strategies for AUGIH (Jairath *et al.*, 2010). No firm conclusions could be drawn from these studies but it should be noted that the first of these small trials (Blair *et al.*, 1986) did indicate an increased risk of rebleeding associated with liberal transfusion, which would be confirmed in a much larger and more rigorous RCT 25 years later.

Two large RCTS have been published since 2013; a phase 3 trial (Villanueva *et al.*, 2013) and a phase 2/feasibility trial (Jairath *et al.*, 2015), which collectively have improved the current evidence base to inform transfusion management of AUGIH. The first study is the seminal phase 3 trial published by Villanueva *et al.* (2013). This was conducted in a specialist gastrointestinal bleeding unit in Barcelona and randomised over 900 patients into an individual patient randomised trial of restrictive (transfusion when $Hb < 70\ g\,L^{-1}$) versus liberal (transfusion when $Hb < 90\ g\,L^{-1}$) RBC transfusion strategies. A restrictive approach to transfusion significantly increased the chance of survival at 6 weeks, reduced the risk of further bleeding and was accomplished with a 37% absolute reduction in the proportion of patients receiving transfusion. The rate of overall adverse events was greater in the liberal transfusion arm (48 versus 40%); the key differences being an increase transfusion-associated circulatory overload (TACO) and transfusion reactions in the liberal arm. The trial included strict protocols of care in terms of the use and timing of endoscopy, pharmacological therapies and frequency of haemoglobin concentration measurements, which should be considered when assessing the generalisability of the results to routine clinical care outside of specialist centres (Carson *et al.*, 2011). Nonetheless, this is the highest quality trial to provide a causal relationship between liberal RBC transfusion after AUGIH and adverse outcome, both in terms of mortality and further bleeding. Caution

Table 1. Characteristics RBC transfusion threshold trials

Author	Design	Location	Intervention	Follow-up	Outcomes reported
Blair *et al.* (1986)	Single centre, parallel group	United Kingdom	Restrictive (80 g L^{-1}) versus no threshold (all received 2 U RBCs)	Not stated	Mortality, rebleeding and number of red cell transfusions
Villarejo *et al.* (1999)	Single centre, parallel group	Argentina	Haematocrit <21% versus haematocrit <28%	Not stated	Mortality, rebleeding, acute myocardial infarction, stroke and duration of hospitalisation
Villanueva *et al.* (2013)	Single centre, parallel group	Spain	Restrictive (70 g L^{-1}) versus liberal (90 g L^{-1})	45 days	Mortality, rebleeding, acute myocardial infarction, stroke, transfusion reaction, acute kidney injury, bacterial infection, number of red cell transfusions and duration of hospitalisation
Jairath *et al.*, (2015)	Multicentre, cluster randomised	United Kingdom	Restrictive (80 g L^{-1}) versus liberal (100 g L^{-1})	28 days	Mortality, rebleeding, acute myocardial infarction, stroke, transfusion reaction, acute kidney injury, bacterial infection, number of red cell transfusions and duration of hospitalisation

RBC, red blood cell.

should be exercised in extrapolating the results to patients with a history of acute coronary syndrome, peripheral vascular disease or cerebrovascular disease, because these were exclusion criteria in the study.

The second trial published in 2015 was a UK, multi-centre, cluster randomised trial of transfusion strategies for AUGIH (Jairath *et al.*, 2015). Hospitals were randomised to either a restrictive or liberal RBC transfusion policy such that all patients presenting with AUGIH were managed according to the randomised policy for a total period of 6 months. The trial was pragmatically designed to otherwise reflect routine clinical care with no exclusions other than patients with exsanguinating bleeding. The main purpose of the study was to evaluate the feasibility and safety of implementing transfusion policies for AUGIH and therefore the results should be considered as per a phase 2 trial. There were high levels of protocol adherence in the trial and a 13% absolute reduction in the proportion of patients receiving transfusion in the restrictive arm. Overall there was no significant difference in any of the clinical outcomes between the two arms. It is notable that there was an excess of deaths in the subgroup of patients in the restrictive arm with ischaemic heart disease, although given the scope of the study and small number of events, this should be considered no more than hypothesis-generating. Nonetheless, any future trials should aim to assess the safety and efficacy of restrictive transfusion patients with cardiovascular co-morbidity. Table 1 summarises existing RBC transfusion trials for AUGIH.

PLASMA TRANSFUSION FOR AUGIH

FFP may be a useful intervention for severe AUGIH by replenishing procoagulant and anti-fibrinolytic factors lost through acute bleeding and by providing a source of fibrinogen to promote haemostasis. The bulk of the evidence for FFP transfusion in haemorrhage comes from studies in the setting of trauma. A recent randomised controlled trial (RCT) in trauma examining 1 : 1 : 1 RBC : FFP : platelet transfusion ratio against a 2 : 1 : 1 ratio demonstrated a decrease in the risk of death from exsanguination, although no improvement in overall mortality (Holcomb *et al.*, 2015). It is unclear whether the results of this trial can be extrapolated to other causes of major bleeding. Specifically, bleeding after trauma is associated with the development of a multifactorial coagulopathy and patients tend to be younger and thus less likely to be susceptible to cardiogenic fluid overload, compared, for example, to elderly patients with acute gastrointestinal bleeding.

In real-life practice, FFP is frequently transfused to patients with cirrhosis and AVH as part of initial resuscitation, with over one-third of patient with AVH receiving this in a national UK audit (Hearnshaw *et al.*, 2010; British Society of Gastroenterology, 2007). In stable cirrhosis, prolongation of the PT is rarely associated with abnormal global assays of coagulation such as thrombin generation (TG) or thromboelastometry (ROTEM), but it is not clear whether the same applies in the setting of acute haemorrhage. Many clinicians prescribe early FFP empirically but the risk–benefit balance between haemostatic correction and potential hypovolaemia are uncertain.

Aside from liver disease, there is evidence that standard FFP doses (12–15 ml kg^{-1}) are insufficient to increase individual coagulation factor levels. A large volume of FFP transfusion could increase bleeding severity and rebleeding via a direct effect on portal pressure. A more dynamic picture of the evolution in coagulation profile during acute haemorrhage, for example using real-time thromboelastography may facilitate a more targeted and rational approach to haemostatic transfusion, although there is insufficient evidence at present to recommend use of these technologies in routine clinical practice outside of the research setting (Hunt *et al.*, 2015).

Until further evidence becomes available, national guidelines should be followed, which recommend FFP transfusion when the international normalised ratio (INR), activated partial thromboplastin time (APTT) or prothrombin time (PT) is greater than 1·5 times the upper limit of normal (National Institute of Health and Care Excellence, 2012). Whilst many centres may empirically follow massive transfusion protocols after AUGIH and thus aim for a ratio of close to 1 : 1 RBC : FFP, we would advocate caution in cases of patients with cardiac failure who may be unable to tolerate large infusion volumes, and also exercise caution in over-transfusing patients with AVH due to the risk of exacerbating portal hypertension.

PLATELET TRANSFUSION FOR AUGIH

Almost half of patients presenting with AUGIB are taking non-steroidal or anti-platelet drugs prior to onset of bleeding (Hearnshaw *et al.*, 2011). The effect of these drugs lasts for the duration of the platelet life span (i.e. 7–10 days) and platelet inhibition can be affected by other factors such as genetic polymorphisms. There is no evidence to support the use of platelet transfusions to patients taking anti-platelet agents who present with major gastrointestinal bleeding. Data from a large clinical audit indeed indicated that platelet transfusion is infrequently administered after AUGIH with only 3% of presentations to UK hospitals receiving this (Hearnshaw *et al.*, 2011).

However in the patient with cirrhosis, thrombocytopenia is prevalent and multifactorial in origin (decreased production, sequestration and increased turnover), therefore platelet transfusion in patients with acute variceal bleeding may be considered physiologically useful. A previous study of critically ill patients with cirrhosis admitted to intensive care units found that platelet transfusion was the only component to significantly improve thromboelastography parameters (Clayton *et al.*, 1995). However, despite both thrombocytopenia and thrombocytopathy, there is some evidence that elevated levels of von Willebrand factor in cirrhosis contribute to primary haemostasis under experimental flow conditions, and it is possible that this compensates for reduced platelet numbers and function (Lisman *et al.*, 2006). However there is to date no interventional study to assess whether platelet transfusion to the actively bleeding patient with cirrhosis promotes haemostasis. Transfusion of any component should be judicious due to the risk of further exacerbating portal pressure through volume overload. Current recommended practice is to transfuse platelets when the platelet count falls below 50×10^9 l^{-1} for a patient with AUGIH (National Institute of Health and Care Excellence, 2012).

Correction of coagulopathy

There has been considerable interest in the importance of recognising and treating coagulopathy after traumatic haemorrhage, since it has been reported to be an independent predictor of mortality (MacLeod *et al.*, 2003; Brohi *et al.*, 2003) with transfusion strategies now focusing on earlier use of plasma in addition to RBCs. In a derived analysis from the UK national audit 16% of presentations met criteria for coagulopathy, defined as an INR > 1·5 (Jairath & Barkun, 2012). Patients with coagulopathy had biomarkers indicative of more severe bleeding and a five-fold increase in risk-adjusted mortality. However, this may simply be a non-specific marker of critical illness or and these data so not imply that correction of coagulopathy would reduce bleeding severity.

Major haemorrhage protocols

The advent of major haemorrhage protocols have resulted in empiric administration of FFP and platelets in ratio with RBCs of 1 : 1. Such massive haemorrhage protocols should not be directly extrapolated to patients with AUGIH without critical consideration of whether the patient truly has major haemorrhage and the potential deleterious consequences of implementing such a protocol. Many patients with AUGIH are elderly with cardiovascular comorbidity and prone to fluid overload. In patients with portal hypertensive bleeding, excessive transfusion volumes risk further elevation of portal pressures and thereby worsening of bleeding.

PHARMACOLOGICAL STRATEGIES FOR AUGIH

Proton pump inhibitors

Pre-endoscopic proton pump inhibitors (PPIs) are widely used in the management of suspected AUGIH (Afif *et al.*, 2007). Maintaining gastric pH above 6 is considered to optimise platelet aggregation and clot formation at sites of mucosal injury. A meta-analysis of six RCTs including 2223 patients comparing PPI to control administrations (placebo or Histamine-2 receptor antagonists) found no evidence that pre-endoscopic administration of PPIs led to a reduction in the most important clinical outcomes following AUGIH, namely rebleeding, mortality or need for surgery (Sreedharan *et al.*, 2010). Therefore it may be most suitable for those patients in whom early endoscopy may be delayed or where endoscopic expertise is not available within 24 h.

Antifibrinolytics

Tranexamic acid (TXA) is a derivative of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine binding sites

on plasminogen molecules. Fibrinolysis could play an important pathological role in AUGIH due to premature breakdown of haemostatic plugs at sites of mucosal injury. A meta-analysis of seven trials, including 1754 patients, demonstrated a 39% relative reduction in mortality in patients receiving TXA (RR 0·61, 95% CI 0·42 – 0·89) compared with a placebo, without increasing the risk of thromboembolic events (Manno *et al.*, 2014). However, the quality of the trials was poor, with most conducted prior to the universal use of endoscopic therapy and high-dose proton pump inhibition, which are key features of current management. The effectiveness and safety of TXA for GI bleeding is uncertain and it should not be routinely recommended for AUGIH under further evidence is available. A large pragmatic RCT of the effects of TXA on death and transfusion requirement following gastrointestinal haemorrhage is now underway in the UK with results anticipated in 2017 (Roberts *et al.*, 2014).

Fibrinogen

Fibrinogen concentrate may be administered as part of a massive transfusion protocol. It can be administered in low volumes, is easy to store and can be kept close at hand for acute haemorrhage. Whereas cryoprecipitate, the other main source of relatively concentrated fibrinogen, must be obtained from a hospital blood bank and thawed before use. A trial of fibrinogen concentrate for coagulopathic patients undergoing aortic surgery demonstrated a reduction in bleeding for those treated with fibrinogen concentrate (Rahe-Meyer *et al.*, 2013). There is no evidence at present to support the use of either cryoprecipitate or fibrinogen concentrate for AUGIH, although the setting where there seems most biological plausibility is in patients with cirrhosis and variceal bleeding where there is both hypo- and dysfibrinogenaemia. Present practice is to maintain the fibrinogen level above 1·5 $g\,L^{-1}$ in AUGIH (National Institute of Health and Care Excellence, 2012) and we suspect that optimising management of fibrinogen levels will be one of the key areas for research in AUGIH in the future, particularly as an intervention for reducing the risk of bleeding.

Factor VIIa

FVIIa results in generation of large volumes of thrombin, which triggers the final common pathway resulting in fibrin formation. In a systematic review of 13 trials containing 2856 patients who were administered FVIIa or placebo for bleeding, no difference in mortality was observed between FVIIa and placebo. In AUGIH, two placebo-controlled trials with of FVIIa for AVH were conducted in patients with cirrhosis (Bosch *et al.*, 2004 and 2008). The first of these trials found no difference in mortality between those treated with placebo or FVIIa (Bosch *et al.*, 2004). The second found no difference in its primary outcome of 5-day mortality (Bosch *et al.*, 2008). Therefore it cannot be routinely recommended for the management of AUGIH.

Reversal of direct oral anticoagulants and warfarin

Warfarin is a coumarin anticoagulant, which inhibits vitamin K-dependent clotting factors (pro-coagulant factors II, VII, IX and anticoagulant proteins: protein C and S). Intravenous vitamin K reverses warfarin within 8 h. When reversal is needed more rapidly, prothrombin complex concentrate (PCC) 25 – 50 $U\,kg^{-1}$ (containing factors II, VII, IX and X) can be administered reversing the effects of warfarin immediately. At present, there are no direct reversal agents for direct oral anticoagulants (DOACs) and endotherapy can be challenging because of increased tissue friability in anticoagulated patients. Activated charcoal can be used if dabigatran has been ingested in the preceding 2 h. Dialysis can also be considered to enhance clearance of dabigatran, but clearly has practical limitations. Studies are underway for agents which will directly reverse the effects of DOACs. Idarucizumab (an anti-dabigatran monoclonal antibody fragment) has been shown to reverse dabigatran in healthy volunteers and shows promising results in a phase 3 trial reversing the effects of dabigatran for patients with severe haemorrhage or who require emergency surgery (Pollack *et al.*, 2015). A trial using Andexan*et al*fa, a reversal agent for factor Xa inhibitors, for patients with acute major bleeding is also underway (NCT02329327). On a different note, DOACs (and in particular dabigatran) should be used with caution in patients with established risk factors for AUGIH including those with previous peptic ulcer disease, chronic renal failure and cirrhosis.

WHAT IS KNOWN ABOUT AUGIH AND TRANSFUSION?.

- AUGIH is one of the leading indications for RBC transfusion in the UK.
- Randomised evidence indicates that restrictive transfusion (threshold 70 $g\,L^{-1}$) leads to more favourable outcomes compared to liberal transfusion.
- Treatment effects are more striking in patients with cirrhosis, likely due to exacerbation of portal hypertension with more liberal transfusion.

WHAT ARE THE FUTURE QUESTIONS?.

- What are the optimal transfusion thresholds in patients with cardiovascular comorbidity?
- What is the optimal target haemoglobin following transfusion for AUGIH?
- Does early administration of TXA reduce the risk of death and rebleeding in patients with AUGIH?
- Is there a role for fibrinogen concentrates in the management of severe AUGIH?

SUMMARY

AUGIH is the one of the most common indications for transfusion of all blood components, yet the evidence base to guide safe

and effective use of these components is limited. For RBCs, RCTs indicate that a restrictive approach to RBC transfusion should be followed, with transfusion indicated at thresholds of $<70 g L^{-1}$, but not higher. However, for other causes of AUGIH further evidence is needed, and particular caution should be applied in patients with comorbidities such as cardiovascular disease. In patients with liver cirrhosis, conventional coagulation indices such as the prothrombin time do not reflect global haemostasis, and these indices should not be used to guide transfusion used in isolation. Although there is little evidence to inform transfusion practice for plasma or platelets after AUGIH, best practice guidelines should be followed, which advocate transfusion when the INR/APTT/PT are greater than 1·5 times the upper limit of normal, or when platelets are $<50 \times 10^9 l^{-1}$. However, risks of these interventions should be considered on an individualised basis, especially in the patient with portal hypertensive bleeding where injudicious volume administration risks elevating portal pressures and worsening of bleeding, and also in those patients with limited cardiac reserve who may not tolerate large volumes of component transfusion. Whilst antifibrinolytics appear to be an effective and safe intervention for AUGIH based upon older trials where they demonstrated a mortality benefit, these are not generalisable to modern-day practice and they should not be routinely recommended until further empirical evidence is available.

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