

Acute Upper Gastrointestinal Bleeding in the United Kingdom: Improving Outcomes

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To my parents, my wonderful wife Dipika and my son Aneesh

“Sapere Aude”

Horace

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Abstract

Acute Upper Gastrointestinal Bleeding (AUGIB) accounts for 7000 deaths in the UK annually and is the single leading indication for transfusion of blood components. A large UK audit in 2007 reported high case fatality and rates of further bleeding. Since many deaths are determined by pre-existing co-morbidity, strategies to improve outcome should be targeted at preventable deaths and therefore focus upon improved control of haemorrhage and prevention of further bleeding, which are investigated in this thesis.

Data for the analyses presented originate from the UK national audit of AUGIB, a laboratory study and a cross sectional survey. Five broad themes were investigated including service provision and timing of endoscopy, the use of transcatheter arterial embolisation (TAE) or surgery for refractory bleeding, the impact of coagulopathy on outcome, management of acute variceal haemorrhage (AVH) and haemostatic derangements after AVH, and the use of red blood cells (RBCs).

Although there was no evidence of a "weekend effect" for mortality, earlier endoscopy (<12 hours) was associated with improved control of haemorrhage in higher risk patients compared to later endoscopy (>24 hours). TAE was an effective and safe modality for refractory bleeding, but the high post-surgical mortality (29%) raises questions about the appropriateness of case selection for surgery. Coagulopathy after non-variceal haemorrhage was associated with a 5-fold increase in risk-adjusted mortality. Further bleeding after AVH was strikingly high (26%) with notable deficiencies in the use of vasopressors, antibiotics and endotherapy. Global assessments of coagulation demonstrated that thrombin generation after AVH was normal, but clot strength was poor with excessive fibrinolysis. Platelets, fibrinogen and antifibrinolytics improved haemostasis *ex vivo* but coagulation factor transfusion had no effect. RBC transfusion practice is variable.

This work on AUGIB provides new data highlighting areas of sub-optimal care, and informs both current practice and research questions for new interventional trials.

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I would like to thank the British Society of Gastroenterology, the Society of Acute Medicine and the Association of Upper Gastrointestinal Surgeons for their help in disseminating the survey in Chapter 9.

Lastly, but most importantly, I would like to thank my family for always allowing me to selfishly pursue my goals in life. Without their guidance, support and tolerance I would not be in the fortunate position I am today.

Statement of originality

All work in this thesis is my own unless otherwise stated. The idea for the theme of this thesis and all of the analyses from the national audit dataset were entirely my own (Chapters 4-7). The first draft of all published manuscripts were written by me and then critically appraised by senior co-authors. All publications were peer reviewed. I acknowledge the work of Brennan Kahan who performed statistical analyses, including logistic regression on imputed data-sets and the fractional polynomial model in Chapter 4.

The idea for the laboratory study, its execution and analysis was entirely my own. Some patients were recruited by research nursing staff but the majority by me personally. All laboratory tests were performed by me and I acknowledge the support of Paul Harrison for showing me how to perform thrombin generation assays and ELISAs and James Beavis for teaching me how to perform coagulation factor assays.

The development of the TRIGGER trial described in the concluding chapter was possible through the guidance of a collaborative multi-disciplinary team which I have lead with the guidance and support of Professor Mike Murphy from the inception of the trial, obtaining funding, design and conduct up to the end of recruitment in the role of joint chief investigator. The trial is now closed to recruitment with 935 participants enrolled and analysis is on-going.

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List of publications and presentations arising from this thesis

Several sections of this thesis have been published in peer reviewed journals as a combination of original articles and review articles. I am the first author of all of these publications. In keeping with copyright laws, copyright transfer agreements have been obtained from the publishers and are included in the appendices. These allow reproduction of part or all of the published material, provided it is clearly acknowledged. In keeping with these agreements, for each publication below, I have indicated which chapter of this thesis it is included in.

Publications

1. ***Jairath V*** and Burroughs AK. Anticoagulation in patients with liver cirrhosis: complication or therapeutic opportunity? *Gut* 2013 Jan 7 [Epub ahead of print]. (leading article).
   Review - Reproduced in part in Chapter 2 with permission from BMJ Publishing Group Ltd.

2. ***Jairath V*** and Barkun AN. Improving outcomes from acute upper gastrointestinal bleeding. *Gut* 2012 Sep;61(9):1246-9 (leading article).
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3. ***Jairath V,*** Martel M, Logan RF, Barkun AN. Why do mortality rates for acute non-variceal upper gastrointestinal bleeding differ around the world?- A systematic review of cohort studies. *Canadian Journal of Gastroenterology*. 2012 Aug 26(8); 537-42.
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4. ***Jairath V*** and Barkun AN. The Overall Approach to the Management of UGIB. *GI Endoscopy Clinics of North America*. 2011 Oct;21(4):657-70.
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5. ***Jairath V,*** Kahan BC, Logan RFA, Hearnshaw SA, Travis SPLT, Murphy MF, Palmer KR. Mortality from Acute Upper Gastrointestinal Bleeding in the UK-does it display a weekend effect? *American Journal of Gastroenterology.* 2011 Sep;106 (9):1621-8.
   Original article- Reproduced in Chapter 3 with permission Nature Publishing Group.

6. ***Jairath V,*** Kahan BC, Logan RFA, Hearnshaw SA, Dore C, Travis SPLT, Murphy MF, Palmer KR. Outcomes following acute nonvariceal gastrointestinal bleeding in relation to time to endoscopy: results from a nationwide study. *Endoscopy* 2012 Aug;44(8):723-30.
   Original article- Reproduced in Chapter 4 with permission from George Thieme Verlag.

7. ***Jairath V,*** Kahan BC, Logan RFA, Hearnshaw SA, Dore C, Travis SPLT, Murphy MF, Palmer KR. National audit of the use of surgery or radiological embolization after failed endoscopic haemostasis for non-variceal upper gastrointestinal bleeding. *British Journal of Surgery* 2012(Dec); 99 (12)1672-80.
   Original article- Reproduced in Chapter 5 with permission from John-Wiley and Sons.

8. ***Jairath V,*** Kahan BC, Stanworth SJ, Logan RFA, Hearnshaw SA, Travis SPLT, Palmer KR, Murphy MF. Prevalence, management and outcomes of patients with coagulopathy following acute non-variceal upper gastrointestinal bleeding in the UK. *Transfusion* 2012 Aug 15. doi: 10.1111/j.1537-2995.2012.03849.x. [Epub ahead of print].
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9. ***Jairath V,*** Kahan BC, Logan RFA, Travis SPLT, Palmer KR, Murphy MF. Red Cell Transfusion Practice in patients presenting with Acute Upper Gastrointestinal Bleeding- A survey of 815 UK Clinicians. *Transfusion.* 2011 Sep;51(9):1940-8.
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National and international Oral Presentations

1. Digestive Disease Week, San Diego, USA (2012). **Enhanced thrombin generation in cirrhotics with coagulopathy and variceal bleeding.**

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7. South Central transfusion meeting, Oxford (2011)- **Transfusion in Major Haemorrhage** (invited talk).

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3. ***Jairath V***, Stanworth S, Curry N, Raja A, Collier J, Harrison P, Murphy M, Barnes E. Rotational thromboelastometry in cirrhosis: the clot thickens! *Journal of Hepatology*, 2011.

4. ***Jairath V,*** Kahan BC, Logan RFA, Travis SPLT, Palmer KR, Murphy MF. Red Cell Transfusion Practice in patients presenting with Acute Upper Gastrointestinal Bleeding-A survey of 815 UK Clinicians. *Gastroenterology*, 2011. ***Poster of Distinction, top 10% of all AGA abstracts.***

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6. ***Jairath V***, Logan R FA, Hearnshaw S A, , Kahan B, Travis S PL, Murphy M F, Palmer K R. What role does surgery play in the modern day management of non-variceal upper gastrointestinal bleeding. *Gut*, 2011. ***Poster of Distinction, top 10% of all BSG abstracts.***

7. ***Jairath V***, Kahan B , Dore C, Meredith S, Llewellyn C, Hearnshaw S, Walsh T, Logan R, Travis S, Palmer K , Murphy M. Uncertainty in transfusion practice

for acute upper gastrointestinal bleeding: implications for clinical trial design. *Gastroenterology*, 2011.

8. ***Jairath V,*** Hearnshaw S, Logan RFA, Travis SPLT, Palmer KR, Murphy MF. Transfusional management of Acute Upper Gastrointestinal Haemorrhage. *Transfusion Medicine* 2010.

9. ***Jairath V***, Logan RFA, Hearnshaw S, Travis SPLT, Murphy MF, Palmer KR. Acute Upper Gastrointestinal Bleeding- Why do patients die? *Gastroenterology*, 2010.

Abbreviations used in this thesis

95% CI	95% confidence interval
ATC	Acute traumatic coagulopathy
AUGIB	Acute upper gastrointestinal bleeding
AUGIS	Association of Upper Gastrointestinal Surgeons
AUROC	Area under the receiver operating curve
AVH	Acute variceal haemorrhage
AVH	Acute variceal haemorrhage
BP	Blood pressure
BSG	British Society of Gastroenterology
CI	Confidence interval
COX	Cyclo-oxygenase
DTIs	Direct thrombin inhibitors
ED	Emergency department
ETP	Endogenous thrombin potential
EVL	Endoscopic variceal ligation
FFP	Fresh Frozen Plasma
FgC	Fibrinogen concentrate
GBS	Glasgow Blatchford Score
GPRD	General Practice research database
H.Pylori	Helicobacter Pylori
Hb	Haemoglobin
HES	Hospital episode statistics
HR	Hazard ratio
HR	Heart rate
HSC	Hepatic stellate cell
HVPG	Hepatic venous pressure gradient
IHD	Ischaemic heart disease
INR	International normalised ratio
IQR	Interquartile range
LOS	Length of stay
LT	Lag time
MAR	Missing at random
MELD	Model for end stage liver disease
MNAR	Missing not at random
NHSBT	NHS Blood and Transplant
NSAIDS	Non-steroidal anti-inflammatory drugs
NVUGIB	Non-variceal upper gastrointestinal bleeding
ONS	Office for national statistics
OOH	Out of hours
OR	Odds ratio
PAR	Protease activated receptor
PCC	Prothrombin complex concentrates
PPI	Proton pump inhibitor
PT	Prothrombin time
PUD	Peptic Ulcer Disease

RBCs	Red Blood cells
RCT	Randomised controlled trial
ROTEM	Rotational thromboelastometry
RR	Relative risk
SAM	Society of Acute Medicine
SRH	Stigmata of recent haemorrhage
TACO	Transfusion associated circulatory overload
TAE	Transcatheter arterial embolisation
TF	Tissue factor
TG	Thrombin generation
TIPSS	Transjugular intrahepatic portosystemic shunt
TRALI	Transfusion related acute lung injury
TXA	Tranexamic Acid
UK	United Kingdom

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1 Chapter One

Introduction, literature review and aims of thesis

1.1 AUGIB – Introduction

Acute upper gastrointestinal bleeding (AUGIB) is defined as bleeding proximal to the ligament of Treitz. It is a common medical emergency which can present with life threatening haemorrhage and an important cause of mortality and morbidity in high, middle and low income countries. The UK incidence is 100-150 per 100,000 adults, accounting for approximately 70,000 hospital admissions each year (Crooks et al., 2011) and is the commonest emergency managed by gastroenterologists. Case fatality in the UK remains high at 10% accounting for almost 7,000 deaths per year (Crooks et al., 2011; Hearnshaw et al., 2011).

Risk factors for AUGIB include older age, socio-economic disadvantage, co-morbidities including liver and renal disease, Helicobacter Pylori (*H.pylori*) infection and several classes of medication including non-steroidal anti-inflammatory agents (NSAIDS), aspirin, cyclo-oxygenase (COX) 2 inhibitors and anticoagulants. 90% of cases in the UK are non-variceal in origin, with 10% of presentations secondary to variceal haemorrhage in patients with liver cirrhosis (Hearnshaw et al., 2011).

Regardless of the aetiology of bleeding, the approach to, and principles of management are broadly similar. These include initial assessment and resuscitation, risk stratification, administration of pharmacological agents prior to endoscopy, timely performance of endoscopy and application of dual endotherapy in high risk lesions, followed by post-endoscopic management. With regards to aspects of initial resuscitation, it is notable that AUGIB is a leading indication for transfusion of red

blood cells (RBCs) as well as other blood components, accounting for 13.7% of all RBCs transfused in England (Wallis et al., 2006). Thresholds for transfusion are controversial and in non-bleeding critically ill patients, a more liberal approach to RBC transfusion has been associated with adverse clinical outcomes (Hebert et al., 1999). Overall, there have been many changes in patient pathways for diagnosis and management of AUGIB over the past decade. The burden of disease for National Health Service Hospitals and care is very high.

Rather than attempting to provide a comprehensive overview of a diverse topic, this chapter provides a literature review of the relevant background information and components of care for AUGIB, which help to put the remaining chapters into context. This includes a summary of risk factors, causative lesions, processes of care and outcomes, before focussing upon management and outcomes specific to the UK. This is followed by a description of the aims of this thesis and an outline of the chapters.

1.2 Risk factors for AUGIB

1.2.1 Age

The percentage of older patients presenting with AUGIB has been increasing rapidly over the last decade in the Western world. A study from Scotland demonstrated a marked increase in admission rates for peptic ulcers in people aged over 74 years, despite a decrease in ulcer incidence overall (Kang et al., 2006). In the recent national UK audit of AUGIB, 63% of presentations with AUGIB were aged over 60 years, with 28% aged over 80 years (Hearnshaw, 2011).

The main reason postulated for this trend is the increasing use of ulcerogenic medications in older patients. Using hospital episode statistics (HES) and community prescription data from the Department of Health, a study in England demonstrated a 460% increase in prescriptions for aspirin (75mg) in between 1990-2000, an increase in NSAID use by 13% and oral anticoagulants by 200% (Higham et al., 2002). Older age has also been established as a risk factor for poorer clinical outcomes. A UK study from 1999 reported crude case fatality rates of twenty times greater in patients over 65 years compared to those aged 30-64 (Higham et al., 2002). A similar observation was reported in a Scottish study, although after adjustment for co-morbid illness, age was no longer found to be an independent predictor of mortality, therefore the presence of co-morbidity was believed to be the main adverse predictor of outcome (Blatchford et al., 2000).

1.2.2 Co-morbid illness

The association between co-morbidity and mortality following AUGIB is well documented in UK populations (Blatchford et al., 1997; Rockall et al., 1996). During

development of the Rockall risk stratification score from the first UK national audit of AUGIB (Rockall et al., 1996), the relationship between 20 co-morbidities and mortality was examined in unadjusted analyses ***(Table 1.1)***. More recently, data from the second UK national audit of AUGIB reported age-standardised mortality for several co-morbidities (Hearnshaw et al., 2011) ***(Table 1.2)***. Both studies found that disseminated malignancy, liver cirrhosis and renal failure were associated with the highest risk of death. Liver cirrhosis in particular is associated with more than a two-fold risk of mortality, further bleeding and need for endoscopic therapy (Lecleire et al., 2005).

Table 1.1: Univariate analyses of co-morbidities associated with mortality in 1993 UK Audit of AUGIB (Rockall et al., 1996)

Co-morbidity	Odds Ratio	95% Confidence Interval
Disseminated Malignancy	11.7	8.28-16.6
Renal failure	10.3	6.96-15.3
Liver failure	8.65	6.01-12.5
Cardiac failure	7.73	5.68-10.5
Pneumonia	7.72	4.80-12.4
Haematological malignancy	6.23	3.91-9.94
Malignancy	6.28	4.0-9.86
Ischaemic heart disease	1.30	3.17-5.81

Table 1.2: Age-standardised mortality by medical co-morbidity in the 2007 UK Audit of AUGIB (Hearnshaw et al., 2011)

Co-morbidity	Odds Ratio	95% Confidence Interval
Liver cirrhosis	2.88	2.36-3.40
Malignancy	2.11	1.75-2.46
Renal failure	1.62	1.32-1.92
Cardiac failure	1.59	1.26-1.92
Stroke	1.50	1.21-1.78
Ischaemic heart disease	1.46	1.25-1.68
Respiratory disease	1.37	1.12-1.62
Dementia	1.31	1.02-1.59

1.2.3 Drugs

Several classes of medications are risk factors for AUGIB. Most are used to prevent or treat common co-morbidities, with some available for routine purchase without prescription.

1.2.3.1 Non-steroidal anti-inflammatories

NSAIDS are commonly prescribed due to their efficacy as a general analgesic, anti-platelet effects and in the treatment of common inflammatory conditions such as osteoarthritis. The incidence of clinically significant upper gastrointestinal complications associated with NSAID use has been shown to approximate 1-2% per year of treatment, or a four-fold increase from that of non-NSAID users (Lee and Cryer, 2011).

NSAIDS induce gastrointestinal injury by either topical or systemic effects. Their topical effects are related to their weakly acidic property, which induces epithelial damage of the intestinal mucosa. Their systemic effects are by virtue of inhibition of COX, which is the rate limiting enzyme in the synthesis of prostaglandins from arachidonic acid.

There are two main isoforms; (1) COX-1 which is constitutively expressed, resulting in prostaglandin synthesis, which in turn stimulates production of mucus and increased mucosal blood flow in gastric mucosa. In addition COX-1 stimulates thromboxane production from platelets, which is important for platelet aggregation as sites of mucosal bleeding; (2) COX-2 is an inducible enzyme and produced in most tissues in response to inflammation, although this has little activity in the human GI tract or on platelets. This has led to the development of COX-2 selective NSAIDS which tend to be

associated with lower rates of GI complications. There is a hierarchy of toxicity with ibuprofen carrying the lowest risk of an upper GI complication (RR 1.9 compared to non-NSAID users) and piroxicam the highest risk (RR 6.3 compared to non-NSAID users).

1.2.3.2 Aspirin, clopidogrel and their combination

Aspirin is used extensively for the primary and secondary prevention of cardiovascular events. Approximately 28% of the 12 million people aged over 60 years in England take aspirin (75mg-300mg). Reduction in ischaemic events comes at a cost of increased major bleeding events; whilst the risk: benefit ratio for secondary prevention is not disputed, there is on-going debate surrounding the benefit of aspirin for primary prevention.

In patients at low risk of gastrointestinal complications, low dose aspirin increases the risk of non-variceal AUGIB by 1.5 to 3.2 fold, and the absolute rate is increased by 0.12% (95% CI, 0.07%-0.19%) per year with a number needed to harm of 833 patients (95% CI, 526-1429) (Laine, 2006). A meta-analysis of RCTs found the rate of AUGIB associated with aspirin use at doses <100mg to be 1.1% (95% CI, 0.9%-1.3%), at doses 100mg-325mg to be 2.4% (95% CI, 2.2%-2.6%) and at doses >325mg to be 2.5% (95% CI, 1.8%-3.1%) (Serebruany et al., 2004).

Clopidogrel is a highly effective antiplatelet drug for the reduction of cardiovascular events, either as an alternative to or in addition to aspirin. Whilst it is not ulcerogenic per se, it increases the risk of bleeding from ulcers or erosions in the GI tract from other causes. The risk of AUGIB on clopidogrel is between 1 and 2 per 100 person years. Patients taking clopidogrel are more likely to develop AUGIB than the general population (RR 2.5) (Ibanez et al., 2006), but less likely than patients on low dose

aspirin (RR 0.7) (Committee, 1996). A pooled analysis of published trials found the incidence of major bleeding resulting in hospitalisation to be 1% with aspirin alone, 0.85% with clopidogrel alone and 1.7% with their combination (Usman et al., 2009). The absolute increase in risk with dual antiplatelet therapy is 1.3% (95% CI, 0.6%-1.9%) compared to clopidogrel alone (Li et al., 2004).

1.2.3.3 Anticoagulants

Anticoagulants are increasingly prescribed for the treatment and prevention of thrombotic complications of cardiovascular disease. These agents do not induce mucosal injury per se but are associated with an increased severity of bleeding. The most commonly prescribed is the vitamin K antagonist, warfarin. The rate of major bleeding (from any source) in RCTs of patients treated with warfarin for atrial fibrillation ranges from 1% to 7.4% per year (Almadi et al., 2011; Levine et al., 2004). A case-controlled study using data from the UK General Practice Research Database (GPRD) reported the adjusted rate ratio for AUGIB in patients receiving warfarin was 1.98 (95% CI, 1.61-2.34); when warfarin was co-administered with aspirin the adjusted rate ratio was 6.48 (95% CI, 3.48-8.32). A further UK case-controlled study examining risk factors for peptic ulcer bleeding reported an odds ratio of 7.8 (95% CI, 2.8-21.5) for oral anticoagulants, with an attributable risk of 300 cases per 10,000 patients aged >60 years diagnosed with AUGIB each year (Weil et al., 2000).

Of possibly greater concern are the novel oral anticoagulant agents, direct thrombin inhibitors (DTIs; e.g. Dabigatran). The attraction of these to patients and healthcare practitioners is likely to be the reduced variability in anticoagulant effects in comparison to warfarin, together with absence of the need for monitoring. Although there was no difference in overall bleeding events between dabigatran and warfarin in large

international RCT in patients with atrial fibrillation (RR 0.93, 95% CI 0.81-1.07) (Connolly et al., 2009), the major concern to gastroenterologists is that, unlike warfarin, the anticoagulant effects of these novel DTIs cannot be acutely reversed (Makris et al., 2013).

1.2.4 Helicobacter pylori infection

H.pylori is one of the most common bacterial infections in humans. It is estimated that more than 50% of the world's population are infected, with infection more commonly acquired at an earlier age in developing countries. A UK population based study of 2437 individuals in 2009 reported a UK prevalence of 26% (Jackson et al., 2009). Faeco-oral and oral-oral routes of transmission are thought to be the most likely explanation for infection (Jackson et al., 2009), although contaminated water may also pose an environmental risk in developing nations.

H.pylori is a recognised cause of acute gastritis, chronic gastritis and gastroduodenal ulceration. A systematic review of 71 studies including 8469 patients reported the mean prevalence of *H.pylori* infection in peptic ulcer bleeding of 72%, although prevalence varied according to geography and concomitant use of NSAIDS (Sanchez-Delgado et al., 2011). In users of aspirin, *H.pylori* increases the risk of AUGIB 2.5 to 4.7 fold (Johnson, 2005), compatible with an ulcerogenic role for *H.pylori* with aspirin acting to provoke bleeding. Eradication of infection improves gastroduodenal ulcer healing, prevents ulcer recurrence and ulcer related complications of further bleeding (Labenz and Borsch, 1994) and perforation (Behrman, 2005).

1.3 Causative lesions

In the UK, data from 2007 indicated that peptic ulcer disease remains the leading cause of AUGIB accounting for 36% of presentations, followed by varices (11%), erosive disease (10%; gastritis and duodenitis), oesophagitis (9%), malignancy (4%), Mallory-Weiss syndrome (2%), vascular anomalies/other (3%) and no cause identified (18%) (Hearnshaw, 2011). In other developed nations, peptic ulcer bleeding is reported to account for 30-59% of cases of AUGIB; these differences may be in part accounted for by differing use of NSAIDs and prevalence of *H.pylori*, although direct comparisons are limited due to differences in case ascertainment and study methodologies.

1.3.1 Changing time-trends in peptic ulcer disease

Globally, there appears to be a decreasing incidence of peptic ulcer disease (PUD) in most countries. The most plausible reason is as a result of the decrease in *H.pylori* infection, especially in developed nations. A study using data from the UK GPRD reported a decline in the prevalence of peptic ulcer disease from 3.3/1000 in 1994 to 1.5/1000 in 1998 (Kang et al., 2002). Similarly, in a study from Scotland, annual prevalence in hospital admissions for PUD decreased from 0.18% in 1982-1984 to 0.10% in 2000-2002 (Kang et al., 2006).

1.3.2 Changing time trends in liver cirrhosis and variceal bleeding

Cirrhosis of the liver is the most severe form of liver disease and the common outcome of different aetiologies and mechanisms of chronic liver injury. It is a major cause of morbidity and mortality globally, accounting for over 800,000 deaths annually worldwide (WHO Mortality Database, 2006). A study using data from the UK GPRD reported a 45% increase in the incidence of cirrhosis in the UK from 1992 to 2001 and a

68% increase in prevalence (Fleming et al., 2008). In 35-44 year olds, there has been an eight-fold increase in men and seven-fold increase in the number of women dying from cirrhosis (Leon and McCambridge, 2006). The increase has been seen in both alcoholic and non-alcoholic cirrhosis. The formation of gastroesophageal varices is a complication of cirrhosis developing in 50% of cases, the rate dependent upon the severity of underlying disease (Kovalak et al., 2007) with subsequent life-threatening acute variceal haemorrhage (AVH) occurring at a rate of 5-15% per year. As a consequence of the rising incidence and prevalence of cirrhosis in the UK, the frequency of variceal bleeding has more than doubled in the interval between two large UK audits of AUGIB between 1993 and 2007 (Hearnshaw, 2011; Rockall et al., 1995).

1.4 Processes of care

The following sections outline processes of care for AUGIB. These are broadly the same whether the aetiology is non-variceal or variceal, although there are some important differences in terms of administration of pharmacological therapy and endoscopic therapy.

1.4.1 Resuscitation and risk stratification prior to endoscopy

The initial priority is of prompt and repeated assessment of airway, breathing and circulation as patients are at risk of haemodynamic shock and airway compromise. Haemodynamic shock is associated with an increased mortality (Blatchford et al., 1997; Rockall et al., 1995) and restoration of circulating volume takes priority over endoscopy. There are no studies comparing initial resuscitation with crystalloid or colloid in patients with gastrointestinal bleeding. Fluid challenge with either product could be used to commence initial volume restoration prior to blood components for NVUGIB, although colloids or albumin are preferred in patients with cirrhosis and ascites. The use of RBCs as part of initial resuscitation and correction of coagulopathy are discussed later in this chapter.

All patients should be risk assessed using well validated prognostic scoring systems such as the Rockall score (Rockall et al., 1996), Glasgow-Blatchford score (GBS) (Blatchford et al., 2000) or the Child-Pugh score for patients with known or suspected liver cirrhosis. Using combination of clinical, laboratory and endoscopic data, these scoring systems facilitate risk stratification and identification of low risk patients suitable for early discharge as well as those patients at high risk for mortality and further bleeding who should receive more intensive monitoring with access to early endoscopy and specialist care. Despite their derivation over a decade ago, external

validation in multiple cohorts, and recommendation in evidence based UK national as well as international guidelines (Barkun et al., 2010) just 19% (1250/6750) of patients were found to have either a Rockall or GBS score documented in clinical charts in the recent UK audit of AUGIB and the Use of Blood. Similar data were reported in the Canadian registry of upper gastrointestinal bleeding and endoscopy (RUGBE) study, where only one out of 15 sites used the Rockall score routinely to stratify patients with NVUGIB and none used the GBS score (Bensoussan et al., 2005). A wealth of observational data supports the benefits of routine use of these scores and they are a simple aspect of care which should be achievable in all patients admitted with AUGIB and could be formally evaluated as components of future studies.

1.4.2 Use of Red Blood Cells

RBCs are usually administered as part of initial resuscitation or for the management of further bleeding. AUGIB is the leading indication for RBC transfusion, accounting for 13.7% of all RBCs transfused in England (Wallis et al., 2006). Their purpose is to restore regional and global oxygen delivery. RBC transfusion is life-saving in exsanguinating patients, but most patients presenting with AUGIB do not have major haemorrhage, or features of hemodynamic compromise. Given that the rates of endoscopic intervention following AUGIB are only in the order of 20-30% (Hearnshaw et al., 2010; Pang et al., 2010), most bleeding will cease spontaneously. RBCs are transfused because the haemoglobin concentration (Hb) has fallen below a threshold at which the physician believes the risks of anaemia to outweigh the risks of transfusion. This is likely to be influenced by multiple factors including the desire to have a "safe" Hb in the event of further bleeding, to reduce symptoms of anaemia after bleeding has arrested, or by patient and clinician related factors. In critically ill patients without

bleeding, a more liberal approach to transfusion has been associated with adverse clinical outcomes (Hebert et al., 1999). It is vital that the evidence base to inform the safe and effective use of RBCs is improved.

1.4.2.1 Evidence for safe transfusion thresholds

Healthy humans can tolerate Hbs as low as 5g/dL without adverse consequences (Weiskopf et al., 1998) and Hbs as low as 7g/dL are safely tolerated in non-cardiac surgery, intensive care and trauma patients (Carson et al., 2002). However 13% of patients presenting with AUGIB in the UK have ischaemic heart disease (IHD) (2007), raising concerns about the safe level of anaemia in these patients. There are limited data indicating that subjects with coronary artery disease may be able to tolerate moderate normovolaemic haemodilution well (Spahn, 2004; Spahn et al., 1996). Lowering the Hb threshold for transfusion in patients undergoing coronary artery bypass surgery from 9 to 8g/dL (Bracey et al., 1999), or from a haematocrit of 30% to 24%, did not result in higher morbidity or mortality (Hajjar et al., 2010). The TRICC trial, a study comparing restrictive versus liberal RBC transfusion in intensive care patients, found no difference in mortality through use of a restrictive transfusion policy (Hb transfusion threshold <7 g/dL) in a subgroup of 257 patients with known IHD (Hebert et al., 2001).

1.4.2.2 Current guidelines for RBC transfusion in AUGIB

Current RBC transfusion practices in AUGIB are based upon consensus opinion. British Society of Gastroenterology (BSG) guidelines recommend RBC transfusion when the Hb is ≤10 g/dL (Palmer, 2002), but a more recent international guideline advocates transfusion when the Hb is ≤7g/dL(Barkun et al., 2010). For those patients with AUGIB secondary to portal hypertension, guidelines recommend maintaining the Hb around 8g/dL (de Franchis, 2010), but not higher.

1.4.2.3 Sources of harm and cost of RBC transfusion

Over the past decade there has been a marked change in critical care and surgical transfusion practice with an increased appreciation of the potentially harmful effects of allogeneic blood transfusion. Research in intensive care (Corwin et al., 2004), cardiac surgery (Murphy et al., 2007) and coronary care (Rao et al., 2004) suggest associations between blood transfusion and adverse patient outcomes, including death, even after adjustment for known confounders. Potential sources of harm from RBCs are poorly understood (Regan and Taylor, 2002). Some, such as transfusion-transmitted infection, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and haemolytic reactions, are well defined but rare. Other possible mechanisms of harm include: [1] adverse effects resulting from changes to RBCs that occur during blood storage (Tinmouth et al., 2006); [2] pro-inflammatory effects of blood transfusion (Ho et al., 2003) and; [3] transfusion of donor leucocytes, although the implementation of universal pre-storage leucocyte-reduction of blood components, implemented as routine practice in the UK in 1999, has reduced this risk (Hebert et al., 2003).

1.4.2.4 UK RBC transfusion practice for AUGIB in 2007

The national audit provided data from 6,750 patients with AUGIB admitted across 208 UK hospitals over a 2 month period (2007; Hearnshaw et al., 2011). The study highlighted areas of significant variation in transfusion practice and inappropriate use of RBCs; for example, 15% of all RBCs were transfused to patients with a Hb >10 g/dL, who were haemodynamically stable. There was substantial clinical uncertainty in transfusion practice in patients presenting with a Hb between 8.1-10 g/dL. In this Hb range 51% of patients received transfusion and 49% did not ***(Table 1.3)***. When patients were then stratified by the absence/presence of haemodynamic instability, the variability

persisted ***(Table 1.4)***. This range represents a genuine area of clinical uncertainty, practice variation, and potential equipoise in the RBC transfusion management of AUGIB.

Table 1.3: Transfusion Practice According to Presenting Haemoglobin in the 2007 National Audit*

First recorded Hb after presentation with AUGIB (g/dL) n=6223	Patients receiving transfusion within 12 hours % (n)	Patients not receiving transfusion within 12 hours % (n)
<7	91 (717)	9 (71)
7.1-8	81 (432)	19 (104)
8.1-10	**51 (604)**	**49 (588)**
>10	9 (324)	91 (3383)

Notes:

**These data were derived by me from the national audit dataset*

These data demonstrates a clear area of uncertainty in clinical practice. The vast majority of patients who presented with a Hb of <8 g/dL received early red blood cell transfusion. At the other end of the spectrum, the vast majority of patients presenting with a Hb of >10 g/dL did not receive early RBC transfusion. However when patients presented with a Hb between 8.1-10 g/dL there is an clear 50/50 divide in practice; this represents a Hb range in which there is genuine clinical equipoise and uncertainty as to the optimum transfusion strategy.

Table 1.4: Transfusion Practice According to Presenting Haemoglobin in the 2007 National Audit Stratified by Haemodynamic Status*

First recorded Hb after presentation with AUGIB (g/dL) n= 6142	Presence of haemodynamic shock†	Patients receiving transfusion within 12 hours % (n)	Patients not receiving transfusion within 12 hours % (n)
<7	Yes	93 (366)	7 (29)
	No	90 (341)	10 (38)
7.1-8	Yes	87 (218)	13 (32)
	No	75 (211)	25 (71)
8.1-10	**Yes**	**63** (295)	**37** (168)
	No	**43** (301)	**57** (407)
>10	Yes	18 (201)	82 (936)
	No	5 (122)	95 (2406)

Notes:

**These data were derived by me from the national audit dataset*

Even in the absence/presence of any features of haemodynamic shock following presentation with AUGIB there still remains a clear area of uncertainty in transfusion practice when patients present with Hb between 8.1-10 g/dL. In those patients who were shocked in this Hb range, 63% were transfused and 37% were not; in those without features of shock 43% were transfused and 57% were not. There is little uncertainty in the other ranges of presenting Hb, regardless of the absence/presence of features of shock.

† Presence of haemodynamic shock defined as either a Systolic blood pressure <100mm/Hg or Heart rate >100 beats per minute.

1.4.2.4.1 Relationship between RBC transfusion, mortality and further bleeding after AUGIB

The relationship between early RBC transfusion, further bleeding and mortality following AUGIB in 4,441 patients from the national audit data-set was examined. After adjusting for the clinical Rockall score and initial Hb, early RBC transfusion was associated with a two-fold increased risk of further bleeding (OR, 2.26; 95%CI 1.76-2.90) and a 28% increase in mortality (OR 1.28; 95%CI 0.94-1.74) (Hearnshaw et al., 2010). Remarkably similar results were observed in a Canadian study of 1,677 cases of AUGIB (Restellini et al., 2012). Whilst these results do not prove a causal relationship, they indicate that a randomised comparison of restrictive and liberal transfusion policies in AUGIB is justified to confirm or refute the findings of these observational studies.

1.4.3 Correction of coagulopathy

In other models of major haemorrhage such as trauma, where haemorrhage is estimated to account for 40% of deaths (MacLeod et al., 2003), there has been considerable recent interest in the importance of recognising and treating coagulopathy soon after presentation. This acute coagulopathy of trauma (ATC) has been reported to be an independent predictor of mortality (Brohi et al., 2003; MacLeod et al., 2003) and current transfusion strategies now focus on earlier use of fresh frozen plasma (FFP) in addition to RBCs, with an apparent survival advantage in observational studies. Whilst the major cause of death following AUGIB is death secondary to cardio-respiratory complications, death due to uncontrollable haemorrhage is reported to account for between 20-25% of cases (Jairath et al., 2010; Sung et al., 2010). In addition to standard multi-modal interventions including high dose proton pump inhibition, therapeutic endoscopy, radiological embolisation or surgery, optimal haemostatic transfusion strategies may help to arrest bleeding. The management of AUGIB shares similar

features to the management of any other cause of major haemorrhage, including the need for timely and adequate resuscitation followed by definitive therapies to control bleeding. However, unlike the trauma literature, there is a paucity of data for AUGIB on the prevalence of coagulopathy, current transfusion management and the association between coagulopathy and patient outcomes. A greater understanding of these factors may highlight key differences in our understanding of ATC, but also open up new therapeutic approaches targeted at reducing the burden of death directly due to haemorrhage.

In a Canadian cohort of 1869 patients with NVUGIB, a presenting International normalised ratio (INR) >1.5 was associated with almost a two-fold increased risk of mortality (OR 1.95, 95% CI 1.13-3.41) after adjustment for confounders but not an increased risk of re-bleeding (Shingina et al., 2011). Another study in patients with a AUGIB, using a historical cohort comparison, suggested that correcting an INR to less than 1.8 as part of intensive resuscitation led to lower mortality and fewer myocardial infarctions in the intervention group (Baradarian et al., 2004). Current guidelines recommend that the presence of a coagulopathy should prompt correction with appropriate blood components in liaison with the transfusion team (e.g. FFP, prothrombin complex concentrates).

The completeness of correction of any coagulopathy should not delay the performance of early endoscopy (Barkun et al., 2010). This is based on recognition of the benefits of early endoscopic intervention and the decreased tissue damage associated with newer ligation haemostatic techniques such as endoscopic clips. Limited observational data also suggest that endoscopic haemostasis can be safely performed in patients with an elevated INR as long as it is not supratherapeutic (*i.e.* > 2.5) (Choudari et al., 1994).

1.4.3.1 Correction of coagulopathy in patients with liver cirrhosis and variceal haemorrhage

The liver is the site of synthesis of all coagulation proteins with the exception of factor VIII, which is also produced in the pulmonary vascular endothelium, and von-Willebrand factor. As a consequence, patients with cirrhosis commonly develop a complex and multifactorial disorder of haemostasis resulting in abnormal standard coagulation indices (e.g. prothrombin time), which have suggested a hypocoagulable profile exists, commonly resulting in administration of blood components both for prophylaxis and treatment of bleeding. The following sections summarise the recent shifting paradigm in our understanding of coagulation derangements in stable liver disease and how these may predispose to haemorrhage.

1.4.3.1.1 Normal coagulation

Like many physiological systems, the coagulation cascade is dependent upon a dynamic interplay between multiple opposing pro- and anticoagulant drivers so as to maintain physiological haemostasis and prevent unwanted episodes of bleeding or thrombosis. The end product of this proteolytic cascade is the generation of thrombin, which cleaves soluble fibrinogen into fibrin to form a blood clot (Coughlin, 2000). This process occurs in several phases.

The *initiation* phase occurs when tissue factor (TF) exposed on cellular surfaces of vascular injury binds circulating factor VIIa, (Morrissey et al., 2012) which leads to small amounts of thrombin production through activated factor X (Xa). At this stage there is insufficient thrombin to activate fibrinogen, therefore a series feedback loops through an *amplification* stage leads to further thrombin generation which is maintained by the *propagation* phase through generation of large quantities of activated factor X.

After the formation of soluble fibrin monomers, activated factor XIII cross-links these to form a stable fibrin meshwork. In order to prevent pathological clot formation, thrombin generation is regulated by the anticoagulant system including proteins C, S and antithrombin. Finally, clot dissolution occurs via activation of the fibrinolytic cascade. Healthy individuals have sufficient quantities of coagulation factors, regulatory proteins and platelets to maintain haemostasis, thus preventing bleeding or thrombotic complications.

1.4.3.1.2 Coagulation in stable liver cirrhosis

Patients with cirrhosis of the liver have multiple defects in components of the aforementioned pathways including deficiencies in both pro- and anticoagulant factors (Tripodi et al., 2009), anaemia (Thachil, 2011), thrombocytopenia (Pradella et al., 2011), hypo and dysfibrinogenaemia (Francis and Armstrong, 1982), as well as evidence of hyperfibrinolysis (Ferro et al., 2009). These derangements, reflected in conventional coagulation indices and haemorrhagic complications seen with cirrhosis, have led to cirrhosis being regarded a prototypical haemorrhagic disorder. However, in very recent years this interpretation has been challenged (Tripodi and Mannucci, 2011), leading to a paradigm shift in understanding, due to increasing evidence of the thrombotic complications associated with cirrhosis (Sogaard et al., 2009; Wu and Nguyen, 2010), such that now cirrhosis is considered as a procoagulant disease state, which may be implicated in the pathogenesis of fibrosis progression. These observations have lead to preliminary interventional trials of anticoagulation in patients with liver cirrhosis, something unthinkable a decade ago.

1.4.3.1.3 Haemorrhagic phenotype of patients with cirrhosis

The bleeding diathesis of patients with cirrhosis is the phenotype that most clinicians are familiar with in their clinical practice. The perception has been that patients with cirrhosis are "auto-anticoagulated", based not only on an abnormal prothrombin time, but also the frequent occurrence of haemorrhagic episodes. Bleeding can occur at multiple sites ranging from trivial to life-threatening including cutaneous, gingival or variceal bleeding and also menorrhagia or epistaxis. Consequently cirrhosis is also a major indication for the transfusion of blood components, not only to treat bleeding but also for prophylaxis of bleeding (Wallis et al., 2006). The most devastating haemorrhagic complication remains variceal haemorrhage. Bleeding from gastro-oesophageal varices is currently understood to be mainly a result of portal hypertension, local vessel wall abnormalities and endothelial dysfunction, but the possible contribution of deranged haemostasis as a precipitant of bleeding or as an aggravating factor is poorly documented.

RCTs showed that recombinant factor VIIa, one of the most powerful procoagulants, was ineffective at controlling variceal bleeding (Bosch et al., 2004; Bosch et al., 2008; Lodge et al., 2005; Planinsic et al., 2005), suggesting that deranged haemostasis - or more specifically a deficiency in coagulation factors - may have a limited role in determining the most common bleeding event observed in cirrhosis. However, this does not preclude the possibility that others components of the coagulation cascade (e.g. platelet function, hyperfibrinolysis) could contribute to bleeding. There is absence of data characterising derangements in haemostasis at the point of presentation with variceal haemorrhage using more global assessments of coagulation, and this is an area requiring further work to improve the understanding of how best to manage abnormal haemostasis during episodes of acute bleeding (Boks et al., 1986).

Factors contributing to this propensity towards bleeding can be considered in terms of defects in pathways of the coagulation cascade and other factors. Thus cirrhosis is characterised by a reduction in synthesis of all procoagulant factors, which worsens as the disease progresses. The exception to this is the powerful procoagulant factor VIII, which shows the opposite trend, which is also synthesized in extra-hepatic sites including the pulmonary vascular endothelium (Jacquemin et al., 2006). Thrombocytopenia is also common and multifactorial, due to a reduction in platelet production, sequestration and increased turnover (Pradella et al., 2011). Platelet levels are important initiators of coagulation since their surface phospholipids provide the platform for assembly of coagulation factors. Whilst platelet numbers and function may be reduced, there is some evidence that platelet hyperactivation may compensate for this (Violi et al., 2011), perhaps in part due to increased circulating platelet derived procoagulant microparticles (Jairath V, 2012; Sayed et al., 2010), but also 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 impair response to bleeding or promote it.

Other factors which promote bleeding include sepsis, endotoxaemia and uraemia. Infection is known to precipitate bleeding and use of antibiotics following variceal haemorrhage has been shown both to reduce severity of bleeding and early further bleeding in randomised trials (Hou et al., 2004; Jun et al., 2006). It is unclear whether the relationship with sepsis is due to alterations in portal haemodynamics or coagulation or indeed, both. Infection has been associated with increased levels of circulating heparinoids in patients with cirrhosis and active bleeding, which may indirectly interfere with coagulation (Senzolo et al., 2007). 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).

1.4.3.1.4 Thrombotic phenotype of patients with cirrhosis

In recent years large scale population based data have documented the propensity towards venous thrombosis in patients with cirrhosis (Ali et al., 2011; Sogaard et al., 2009; Wu and Nguyen, 2010), a phenotype far less recognized by most clinicians. This increased risk applies to both ambulant as well as hospitalised patients. Thrombosis in a vascular bed can occur through a defect in any component of Virchow's triad – hypercoagulability, vascular injury or circulatory stasis. Thromboses in the portal and mesenteric vasculature are not uncommon in cirrhosis (Tsochatzis et al., 2010), and are thought to be mainly due to sluggish blood flow through the liver due to intrahepatic portal hypertension. Inherited thrombophilias may also play a role (e.g. inherited deficiency of antithrombin, protein C or S), but evaluation of these is complicated by concomitant acquired deficiency and routine anticoagulation is not necessarily effective (Senzolo et al., 2012).

However, the aforementioned population studies also describe an increased risk of peripheral venous thrombotic events such as deep vein thrombosis and pulmonary emboli. Aside from derangements in the coagulation cascade, other recognised factors may contribute towards the risk of thrombo-embolism including immobility, hospitalisation and increasing age. It is unclear why prothombotic disorders predispose to clotting in particular regions of vascular beds and it is possible that the selectivity of the thrombosis in a particular vascular bed may be related to pro- and anticoagulant activity of endothelial cells in that particular segment of vasculature (Rosenberg and Aird, 1999). Occurrence of an increased risk of these macro-thrombotic complications

in cirrhosis is counterintuitive, due to the haemorrhagic complications observed in clinical practice, as well as conventional coagulation indices suggesting hypocoagulation. The occurrence of an increased risk of macro-thrombotic events as well as portal and splanchnic venous thrombosis presents a clinical challenge due to the perceived risk of therapeutic or prophylactic anticoagulation in patients at high risk of bleeding from varices or other sites, as well as the potential difficulty in monitoring anticoagulation.

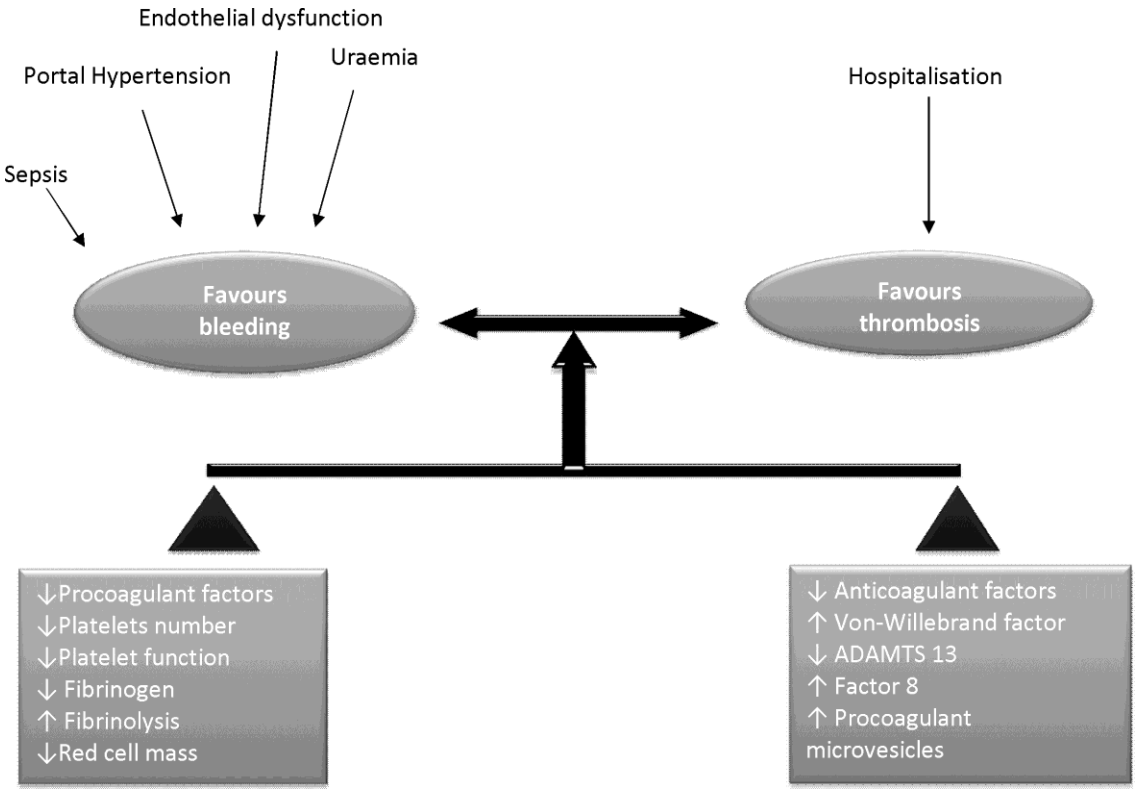
1.4.3.1.5 Measures of coagulation status and rebalanced haemostasis

The paradox between occurrence of bleeding and thrombosis may be better appreciated with an understanding of the tests used to measure deranged coagulation. Conventionally, assessment of coagulation status is based upon evaluation of the prothrombin time (PT) and activated partial thromboplastin time (APTT). These are cheap, simple and widely available tests, yet are crude and static measures of coagulation. The PT is only sensitive to thrombin generation with respect to procoagulant factors and is insensitive to the inhibition of thrombin by anticoagulant factors (Tripodi and Mannucci, 2007). Therefore it is not surprising that the PT does not predict the risk of bleeding from varices, nor after invasive procedures, in patients with cirrhosis (Boks et al., 1986; Segal and Dzik, 2005; Terjung et al., 2003), but nonetheless the PT is routinely used by those performing invasive procedures and stipulated in guidelines as a threshold for the prophylactic use of blood components.

More accurate global tests of coagulation include thrombin generation assays, which have shown that plasma from patients with cirrhosis appears to be hypercoagulable in comparison to healthy controls (Gatt et al., 2010; Tripodi et al., 2009), and thromboelastography. This is explained by the concomitant decrease in anticoagulant

factors as well as procoagulant factors in cirrhosis and relative resistance to thrombomodulin. This has lead to the concept of "rebalanced haemostasis" (Lisman and Porte, 2010), albeit a balance which is precarious and may lead to bleeding, thrombosis or even both, in the setting of an appropriate trigger, such as infection ***(Figure 1.1).***

Figure 1.1: Factors promoting bleeding and thrombosis in liver cirrhosis.



*Whilst haemostasis appears to be at least rebalanced in cirrhosis, this balance is believed to be precarious and can easily be tipped towards either a pro-haemorrhagic or pro-thrombotic phenotype in the presence of an appropriate trigger.

1.4.3.1.6 Evidence of hypercoagulation as a mediator of fibrosis

As well as the main effector of the coagulation cascade, thrombin also elicits a number of cellular effects through a family of G-protein coupled receptors known as protease activated receptors (PARs) (Fiorucci et al., 2004). Through these, thrombin stimulates proliferation of hepatic stellate cells (HSCs), key mediators of liver fibrogenesis. Thrombin receptors are constitutively expressed in the liver and expression of thrombin receptors is upregulated during acute and chronic liver injury (Marra et al., 1995; Marra et al., 1998). Excessive thrombin generation, as recently described in plasma based assays in liver disease, may be directly implicated in fibrogenesis through activation of HSCs; inhibition of thrombin generation is therefore a potential target for anti-fibrotic interventions (Calvaruso et al., 2008).

In addition to macro-thrombotic events described earlier, micro-thrombotic complications occur within the liver parenchyma, with a typically more indolent course. Occlusion of intra-hepatic vasculature may lead to localised ischaemia and infarction, a process coined "parencyhmal extinction", based upon histological findings in explanted human livers (Wanless et al., 1995). Intra-sinusoidal, activated platelet aggregates have also been demonstrated adjacent to foci of hepatic injury (Wanless et al., 1995), with levels correlated with the peripheral platelet count, implicating consumption of platelets by cirrhotic livers as a potential contributor to thrombocytopenia. Pro-thrombotic risk factors, such as anti-thrombin deficiency, have also been associated with more advanced fibrosis in patients with chronic viral hepatitis (Papatheodoridis et al., 2003) and in patients with non-alcoholic fatty liver disease (Papatheodoridis et al., 2009).

These observations have led to a seminal, phase II, open-labelled RCT of LMWH versus usual care in patients with advanced cirrhosis at risk of portal vein thrombosis (Villa et al., 2012). The anticoagulated group had significantly better outcomes, namely

a lower incidence of portal vein thrombosis (9% vs. 28% at 2 years) and decompensation (12% vs. 59% at 1 year) and improved overall survival (60% vs. 40%), with no haemorrhagic events in the anticoagulated group. Interestingly, the incidence of bacterial infection was also lower in the anticoagulated group, as were markers of bacterial translocation, raising the possibility that improved intestinal microcirculation due to anticoagulation could reduce bacterial translocation, which is especially relevant in cirrhosis, given the established role of sepsis as a precipitant for variceal bleeding. This proof of concept study of prophylactic anticoagulation in advanced liver disease needs to be confirmed in a definitive phase III RCT (Tsochatzis et al., 2012), which ideally should be multi-centred, placebo controlled and with central, masked adjudication of the endpoints.

1.4.4 Pharmacological therapy pre-endoscopy

The evidence-based use of pharmacological therapy before endoscopy varies according to whether or not the suspected source is non-variceal (majority of cases in UK) or variceal in patients with liver cirrhosis.

1.4.4.1 For NVUGIB

For non-variceal bleeding, there is evidence for the net benefits associated with three main classes of drugs before endoscopy - proton pump inhibitors (PPIs), antifibrinolytics and prokinetics. A Cochrane meta-analysis of 6 RCTs including 2223 patients presenting with unselected AUGIB comparing PPI with control administrations (placebo or H2RAs) demonstrated significant reductions in the proportion of patients with high risk stigmata at endoscopy, as well as a reductions in the need for endoscopic therapy (Sreedharan et al., 2010). Whilst they did not lead to reductions in the key

endpoints of further bleeding, mortality or need for surgical intervention, downstaging of endoscopic stigmata has obvious benefits. In practice, there appears to be uncertainty amongst UK clinicians as to the benefit of PPI's pre-endoscopy. In the 2007 national audit 43% of patients presenting with all-cause UGIB were prescribed a PPI pre-endoscopy, with similar figures (47%) in the Canadian RUGBE database (Bensoussan et al., 2005).

More convincing evidence of benefit comes from a meta-analysis of RCTs of 7 RCTs comparing TXA with placebo in 1754 patients with AUGIB found a 39% relative reduction in mortality in patients prescribed TXA compared to controls (RR 0.61, 95% CI 0.42-0.89) (Gluud et al., 2008). However there is limited evidence of its use in current practice. In the UK audit of AUGIB in 2007 only 18/6750 patients were prescribed TXA. The disparity between the evidence base and its use in practice may reflect uncertainties about the generalisability of the published trials, as many were conducted prior to the era of PPI and routine endoscopic therapy.

Finally, quality of endoscopy can be adversely affected by poor visibility in patients requiring urgent endoscopy with AUGIB due to the presence of blood in the gastric lumen. Pre-endoscopic administration of erythromycin or metoclopramide has been shown in a meta-analysis of 5 RCTs to reduce the need for repeat endoscopy in patients with UGIB (OR 0.55; 95% CI, 0.32-0.94) (Barkun et al., 2010). This is an important adjunct to treatment in terms of the ability to make a diagnosis, apply definitive therapy and avoid unnecessary exposure of patients to repeat procedures; recent meta-analyses have even suggested a resultant decrease in hospital stay therefore it should be used routinely in higher risk patients who are likely to have blood in their stomach, whether suspecting a non-variceal or variceal source (Altraif et al., 2011; Barkun et al., 2010).

1.4.4.2 For AVH

For patients with suspected acute variceal haemorrhage (AVH), intravenous antibiotic prophylaxis is an integral part of therapy and should be administered from admission and have been shown to confer up to a 20% reduction in all cause mortality and a 50% reduction in further bleeding following AVH (Chavez-Tapia et al., 2010; de Franchis, 2010). A meta-analysis identified fifteen RCTs comparing several vaso-active drugs (vasopressin, terlipressin, octreotide, somatostatin) to endoscopic sclerotherapy and found that vasopressors were as effective as sclerotherapy in terms of failure to control bleeding and mortality (D'Amico et al., 2003).

Terlipressin is a synthetic analogue of vasopressin with a longer biological half-life and is the preferred agent in the UK and is the only pharmacological agent shown to confer a reduction in mortality after AVH. A Cochrane meta-analysis of seven RCTs demonstrated that terlipressin confers a 34% relative reduction in mortality (RR 0.66, 95% CI 0.49-0.88) compared to placebo in patients with AVH (Ioannou et al., 2003) and reduced failure to control bleeding (RR 0.63, 95% CI 0.45-0.89). Both antibiotics and vasopressors should be continued for 3-5 days after the diagnosis is confirmed.

1.4.5 Use of Endoscopy

Cornerstone to the management of AUGIB is timely access to diagnostic, and where necessary, therapeutic endoscopy. This permits risk stratification, early discharge of low risk patients and application of endotherapy and a higher level of care for those with high risk lesions. The procedure should be performed by endoscopists skilled in all modalities of haemostasis in appropriate clinical areas and ideally with skilled support staff available, especially important when emergency endoscopy is to be performed out of working hours.

1.4.5.1 Timing of endoscopy

Whilst the effectiveness of therapeutic endoscopy in reducing mortality, further bleeding and the need for surgery for NVUGIB was established almost twenty years ago (Cook et al., 1992; Sacks et al., 1990), it is surprising that the optimal timeframe for the performance of endoscopy remains unclear, not only in relation to patient outcomes but also in terms of the economic implications of providing timely access to endoscopy around the clock. It would seem logical that patients at high risk of further bleeding and death should be offered earlier endoscopy, which may have the potential to prevent further bleeding and improve clinical outcomes.

Consensus guidelines both from the UK and internationally recommend that all endoscopies for AUGIB should be performed within 24 hours of presentation with bleeding (Barkun et al., 2010), but noted no additional benefit associated with urgent (<12 hours) vs. early endoscopy (>12 hours) in unselected patients with AUIGIB. Disappointingly, in 2007 only 50% of all patients presenting with AUGIB in the UK underwent endoscopy within 24 hours of presentation (a figure which had not improved from the previous audit 14 years earlier), probably related in part to the lack of 24 hour

provision of emergency endoscopy in 48% of hospitals at the time the audit was conducted (Hearnshaw et al., 2010).

To date, no study has been able to demonstrate an association between earlier endoscopy and a reduction in mortality in higher risk patients, although there is evidence of improvement in other important clinical endpoints. Besides being a marker of quality of care (Cipolletta et al., 2002), it allows prompt risk stratification and early discharge of those patients with low risk endoscopic stigmata and no serious concurrent co-morbidity (Cipolletta et al., 2002). Secondly it may enable early and targeted endoscopic haemostasis in higher risk patients who are actively bleeding or with high risk stigmata of bleeding and therefore potentially facilitate earlier control of bleeding and reduce further bleeding. Thirdly it has been shown to reduce length of hospital stay and the number of units of blood transfused in both low and high risk groups (Cipolletta et al., 2002; Hay et al., 1997; Lee et al., 1999; Rockall et al., 1996; Spiegel et al., 2001).

However, there is a paucity of data on the benefit of more urgent endoscopy (i.e. before 24 hours), especially in higher risk patients who require endotherapy. Several cohort studies have shown that urgent endoscopy (defined differently in all studies ranging from within 2 to 12 hours) in unselected patients with AUGIB did not improve any clinical outcomes and the results have been summarised in a systematic review (Spiegel et al., 2001). Three RCTs have compared urgent versus early endoscopy; Lin *et al* compared endoscopy <12 hours to >12 hours (Lin et al., 1996); Lee *et al* compared endoscopy performed in the emergency department versus elective endoscopy (Lee et al., 1999) and Bjorkman *et al* compared endoscopy within 6 hours versus 48 hours (Bjorkman et al., 2004). These studies reported no difference in the outcomes of further bleeding or mortality through urgent endoscopy, although all three studies were

underpowered to detect a difference, likely reflective of the logistical challenges inherent in these trials. Further studies are needed to establish the effectiveness of urgent endoscopy, especially in higher risk patients.

1.4.5.2 Endoscopy service provision and the "weekend effect"

An increased mortality in patients presenting to hospital at weekends has been found in a number of acute medical and surgical conditions, an observation which has been termed the "weekend effect" (Barba et al., 2006; Barnett et al., 2002; Becker, 2007; Bell and Redelmeier, 2001; Cram et al., 2004; Ensminger et al., 2004; Kostis et al., 2007; Saposnik et al., 2007). A large retrospective analysis of over 14 million admissions to NHS hospitals for all conditions in 2009-10 using hospital episode statistics linked to mortality data from the office of national statistics found an increased risk of death within 30 days for admissions on the weekend compared to the weekday (HR for Sunday vs. Wednesday 1.16, 95% CI 1.14-1.18, $p<0.001$), after extensive adjustment for co-morbidity and other relevant confounders (Freemantle et al., 2012). These findings have contributed to the debate around redesigning the NHS to provide a weekend service similar to other days of the week.

This is especially relevant to the management of AUGIB, where provision of "around the clock" access to emergency endoscopy seven days a week is an important pre-requisite to perform endoscopy within 24 hours, or sooner, for all patients. Two large cohort studies from the United States and one from Wales have reported a weekend effect for mortality following AUGIB, with 10-20% increased mortality for patients admitted with AUGIB at weekends compared to weekdays (Ananthakrishnan et al., 2009; Button et al., 2011; Shaheen et al., 2009). Possible explanations include lower staffing levels, less senior staff, differing patient characteristics and a lower likelihood

that invasive procedures such as endoscopy will be undertaken at weekends. Given that endoscopic therapy reduces further bleeding and mortality, the inadequate emergency endoscopy service provision at weekends in UK hospitals has the potential to adversely impact upon clinical outcomes.

1.4.5.3 Endoscopic therapy

1.4.5.3.1 For NVUGIB

Which therapies?

Endoscopic therapy for NVUGIB can be broadly divided into injection (e.g. adrenaline, tissue adhesives, alcohol), mechanical (metallic clips, endoloops, rubber band ligation), thermal (heather probe or electrocoagulation) or disruptive (emerging nanopowder sprays). All patients with high risk stigmata of recent haemorrhage (SRH) at endoscopy should receive endoscopic therapy. SRH are divided into actively bleeding lesions (arterial, spurting, oozing) or recent haemorrhage (non-bleeding visible vessel, adherent clot without other SRH, or flat, dark sloughs or spots) (Kovacs and Jensen, 2002).

Single or dual modality?

Whilst monotherapy with adrenaline alone is more effective than medical treatment alone in patients with high risk stigmata, there is overwhelming evidence of the benefit of adding a second modality of treatment in patients with bleeding ulcers and high risk stigmata (non-variceal) in terms of reducing the subsequent risk of further bleeding, surgery and mortality, independent of which second procedure is added to adrenaline injection. A Cochrane review of RCTs comparing combination therapy vs. single therapy with adrenaline identified 17 studies and 1763 patients; addition of a second modality to adrenaline reduced the rate of re-bleeding (regardless of which second modality was used) from 18.8% to 10.4% (OR 0.51; 95% CI 0.39-0.66), emergency

surgery from 10.8% to 7.1% (OR 0.63; 95% CI 0.45-0.89) and mortality from 5% to 2.5% (OR 0.50; 95% CI 0.30-0.82) (Vergara et al., 2007). Whilst the evidence base for this is derived predominantly from trials of peptic ulcer bleeding, the same broad principles of endoscopic techniques apply to other focal lesions with SRH e.g. Dieulafoy lesions, Mallory-Weiss tears.

Despite the strong evidence base, there are surprising shortfalls in translating this into clinical practice. In the UK audit in 2007, 74% of those with high risk stigmata received any endoscopic therapy (a figure which was similar to the previous audit in 1993), and only 38% received dual endoscopic therapy (Hearnshaw et al., 2010). Similar results were seen in the Canadian RUGBE data-base where 72% of patients with any stigmata received any modality of endoscopic therapy with only 34% of those with high risk receiving dual endotherapy (Barkun et al., 2004). It is unclear why there are striking deficiencies in the application of endoscopic therapy and specifically dual endoscopic therapy in patients with high risk lesions, and the reasons for this are difficult to ascertain from retrospective studies. The use of endoscopic therapy, as well as specifically dual endotherapy in lesions with high risk stigmata, seems a key parameter upon which longitudinal studies should monitor future improvements in care.

1.4.5.3.2 For AVH

Endoscopic therapy is recommended in any patient presenting with AUGIB and oesophageal varices which show signs of active bleeding, a “nipple sign”, clot on a varix or varices without any other identifiable source of bleeding (de Franchis, 2010). Endoscopic options include endoscopic variceal ligation (EVL) or sclerotherapy. EVL involves application of elastic bands around varices in the distal 5-7cm of the oesophagus and they subsequently undergo thrombosis and fibrosis. Endoscopic

sclerotherapy involves injecting a sclerosant agent (e.g. ethanolamine) either into or adjacent to the varix, using a freehand technique and may be less technically challenging in the setting of active spurting haemorrhage. Complications of sclerotherapy include oesophageal ulceration, strictures, mediastinitis, bacteraemia, and fever. A meta-analysis of seven RCTs confirmed EVL to be superior to sclerotherapy with an OR 0.52 (95% CI; 0.37-0.74) for further bleeding and 0.67 (0.46-0.98) for mortality (Laine and Cook, 1995) and is associated with fewer local complications and faster obliteration of varices.

Consensus guidelines recommend EVL as the preferred treatment with sclerotherapy reserved in cases where this may be challenging (de Franchis, 2010). Combination therapy of vasopressor and endoscopic therapy is more effective than endoscopic therapy alone for control of initial bleeding and 5-day haemostasis (Banares et al., 2002). Gastric varices do not respond to band ligation or sclerotherapy; endotherapy with tissue adhesive is recommended for acute bleeding from isolated gastric varices or gastro-oesophageal varices that extend beyond the cardia (GOV type 2). In the UK audit in 2007, only 64% of patients who had bled from varices actually received endoscopic therapy, although it is difficult to ascertain retrospectively the decision processes involved.

1.4.5.4 Second look endoscopy

The risk of further bleeding after primary haemostasis in patients with high risk lesions ranges from 10-25%. This lead to a concept that a systematic, pre-planned repeat endoscopy performed within 24 hours of the index endoscopy may reduce further bleeding by routine application of further endotherapy. A meta-analysis of four RCTs compared systematic second look endoscopy and re-treatment within 24 hours of the

index procedure versus routine expectant management. The routine second look was associated with a reduced risk of further bleeding (RR 0.33, 95% CI 0.1-0.96), although the absolute risk was small at 6.2%; there was no impact upon mortality or need for surgery. However these trials used monotherapy with adrenaline alone and pre-dated high dose PPI infusions which reduce further bleeding in high risk patients, so the practice cannot be routinely recommended.

1.4.6 Managing further bleeding

Despite advances in endoscopic and pharmacological therapy over the past two decades, further bleeding occurs in 7-15% in those with NVUGIB (Barkun, 2004; Hearnshaw, 2011; Marmo et al., 2008) and 15-30% in those presenting with AVH (Bambha et al., 2008; Chalasani et al., 2003; Hearnshaw et al., 2011). These figures have surprisingly shown little improvement in longitudinal UK studies (Hearnshaw et al., 2011; Rockall et al., 1995). Further bleeding is defined as either persistent bleeding at the end of the index endoscopy or recurrent bleeding despite achieving endoscopic haemostasis at the index endoscopy (Barkun et al., 2010). Failure of endoscopic treatment has been found to be the strongest predictor of subsequent death within 30 days in a large prospective cohort study from Italy (OR for death 11.4, 95% CI 1.4-24.1, p=0.05) (Marmo et al., 2008).

1.4.6.1 Repeat endoscopy

Repeat endoscopy and endotherapy is usually the next line of intervention in patients who experience clinically significant further bleeding and are considered candidates for on-going active treatment. The evidence base for this arises from a single centre RCT from Hong Kong which randomised 92 patients with recurrent peptic ulcer bleeding to

endoscopic retreatment or surgery (Lau et al., 1999). All patients in the trial had received one endoscopic therapy and initial haemostasis. Endoscopic retreatment (dual therapy) was successful at achieving haemostasis in 35/48 patients (73%) and was associated with fewer complications than those allocated to surgical intervention (p=0.03). Mortality in the endoscopy group occurred almost exclusively in those who failed second endoscopy and thus went for surgery anyway. There was no difference in mortality, duration of hospitalisation or use of blood transfusion between the two groups. Despite there being no difference in mortality, the authors concluded that repeat endoscopy should be performed before referral to surgery since the risks associated with surgery (complications associated with anaesthesia and surgery in patients usually with significant co-morbidity) outweigh those of repeat endoscopy. The study has never been reproduced and its external validity is limited since it arises from a single centre of expertise.

1.4.6.2 Salvage procedures when endoscopic therapy fails

Despite supportive care, pharmacological therapy and repeat endoscopy with application of additional haemostatic modalities, patients may still experience uncontrollable haemorrhage. The role of surgery as a salvage measure in these situations is well established. In more recent years, however, there has been renewed interest in transcatheter arterial embolisation (TAE) as a minimally invasive alternative to surgery.

1.4.6.2.1 Surgery for NVUGIB

Before the advent of therapeutic endoscopy, 30-50% of patients with significant AUGIB required emergency surgery to control haemorrhage with an associated case fatality of 10-30%. Even 2-3 decades ago, the reported use of surgery to control AUGIB

was in the order of 15-20% (Dronfield et al., 1982; Jones et al., 1973; Masson et al., 1996). A study from the UK reported significant reductions in rates of surgery over a 20 year period (1982-2002) (Kang et al., 2006) with similar trends noted in Canada where there has been a reduction in the rates of surgery from 7.1% to 4% during the period 1993-2003 (Targownik and Nabalamba, 2006). Complication rates are likely to be high by virtue of the pre-selection of patients for surgery who have already failed medical and endoscopic options, have received multiple transfusions with the associated immunological insult and with reduced physiological reserve to withstand the stress of major surgery. A recent single centred study from the UK reviewed the surgical management of 53 cases of surgery for AUGIB between 1995-2007 (Clarke et al., 2010). The overall post-operative complication rate was 56%, with 15% experiencing further bleeding despite surgery and 10% died.

Reductions in the use of surgery are largely attributable to improved supportive care and high dose acid suppression, but mainly due to the effectiveness of endoscopic therapy. Nonetheless, expertise in the surgical management of AUGIB remains an integral part of any team managing AUGIB. There are no RCTs comparing different surgical techniques. Choice of surgery is guided by anatomy and aetiology of bleeding, although most surgeons will now perform more conservative surgery for bleeding peptic ulcers. In most circumstances control of haemorrhage is obtained by oversewing the bleeding artery (in most cases the gastro-duodenal artery following PUB) with a non-absorbable suture material. Limited resection of ulcers is usually to rule out malignancy, although giant ulcers in the more proximal stomach may still require partial gastrectomy with gastrojejunostomy.

1.4.6.2.2 TAE for NVUGIB

In recent years TAE has become more widely available as a minimally invasive alternative to surgery. It was first described for the management of NVUGIB in 1972 (Rosch et al., 1972) and its success has been well documented in a review of several single-centre case series (Loffroy and Guiu, 2009), although there have been no multi-centre studies describing its use or outcomes. The technique involves selective catheter-directed embolisation of bleeding vessels with the potential advantage of avoiding general anaesthesia and laparotomy in critically unwell, elderly patients. The aim of the procedure is to selectively reduce blood supply to the source of bleeding whilst maintaining sufficient collateral supply to maintain tissue viability. Arterial catheterization is performed under fluoroscopic guidance and feeding arteries in the bleeding area selectively catheterised. Once a bleeding focus is identified with contrast extravasation, thrombogenic material is injected including foam, coils, gel and glue. Embolisation is generally performed distally in order to occlude across the bleeding site, thereby reducing the chances of collateral blood flow leading to further bleeding. Radiological confirmation of bleeding is seen in 40-60% of cases and technically successful embolisation with cessation of bleeding has been reported in 72 to 100% in case series (Burke et al., 2007; Loffroy et al., 2010; Loffroy et al., 2008).

Complications after TAE relate to the angiography or the actual embolisation. The most serious complication is organ infarction or inadvertent embolisation of non-target organs (e.g. spleen) (Sudheendra et al., 2011). A review of 819 cases of TAE reported a complication rate of 9%, although intestinal ischaemia is relatively rare due to due to the rich collateral blood supply to the stomach and duodenum (Loffroy and Guiu, 2009). Although there are reports of acute ischemia post-embolisation, most cases are thought to present later as duodenal stenosis (Lang, 1992) after embolisation of the gastro-

duodenal artery. Risk factors associated with this are use of embolic agents such as cyanoacrylate glue or a history of previous surgery in this area (Shapiro et al., 1981). Mortality after TAE from single centre series range broadly from 10-45%, similar to those reported after surgery for PUB, although in most cases mortality is a result of concomitant co-morbidity and complications of the bleed (e.g. aspiration).

1.4.6.2.3 Surgery versus TAE for NVUGIB

There are no randomised comparisons of TAE versus surgery after failed endoscopic haemostasis and its place in the current treatment algorithm as the first alternative treatment of choice in managing further bleeding after failed endoscopic haemostasis remains unclear, until further data is available. The choice is likely to be dictated by local availability and expertise.

1.4.6.2.4 Radiological or surgical shunting for refractory AVH

Despite pharmacological and endoscopic therapies, further bleeding occurs in up to 20% of cases after AVH and an elevated hepatic venous pressure gradient of more than 20mmHg is predictive of treatment failure (Moitinho et al., 1999). Rescue therapies include porto-systemic shunting in the form of shunt surgery or TIPSS (Transjugular intrahepatic porto-systemic shunt), which reduces portal hypertension by creating a communication between the hepatic vein and portal vein. A Cochrane review of 22 RCTs evaluating 1409 patients compared the effects of shunts (surgical or TIPSS) with endoscopic therapy (sclerotherapy and/or banding) for prevention of variceal further bleeding (Khan et al., 2006); all shunts lead to a reduction in further bleeding (OR 0.24, 95% CI 0.18-0.30) at the cost of increased encephalopathy (OR 2.07, 95% CI 1.59-2.69), although conferred no survival advantage compared to endotherapy alone. The

choice is left to local expertise, although TIPSS has obvious advantages in avoidance of surgery.

TIPSS provides haemostasis in over 90% of cases and new data have emerged from an RCT reporting that early use of TIPSS (within 72 hours of bleeding) routinely after AVH in patients who have received endotherapy and vaso-active drugs significantly reduces treatment failure and mortality, compared to vasoactive drugs plus endoscopic therapy alone (Garcia-Pagan et al., 2010). TIPSS can also provide longer term definitive haemostasis and newer PTFE-covered stents improve shunt patency without increasing the risk of hepatic encephalopathy. Transplantation is the only treatment which definitely corrects both portal hypertension and liver dysfunction, although the indication for liver transplantation is end-stage liver disease rather than variceal bleeding.

1.4.7 Post-endoscopy care

1.4.7.1 For NVUGIB

1.4.7.1.1 Proton Pump Inhibitor (PPI):

High dose intravenous PPI therapy (e.g. a PPI at a dose of 80mg bolus dose followed by 8mg/hour infusion over 72 hours) should be administrated to patients with high risk stigmata who have received successful endoscopic therapy. This recommendation is based upon a meta-analysis of RCTs including 5792 patients in which PPI therapy reduced the incidence of further bleeding (OR 0.45, 95% CI 0.36-0.57) and need for surgery (OR 0.56, 95% CI 0.45-0.70), but not mortality (OR 0.90, 95% CI 0.67-1.19) (Leontiadis et al., 2006). At present there is insufficient evidence to recommend lower doses or duration of PPI therapy and oral regimens due to methodological limitations in related head-to-head trials (Barkun et al., 2009; Calvet et al., 2010).

1.4.7.1.2 Test and treat for Helicobacter Pylori:

All patients with bleeding peptic ulcers should be tested for *H.pylori* and receive eradication therapy if it is positive. A meta-analysis has shown that eradication of *H.pylori* was more effective than PPI therapy alone in prevention of recurrent bleeding from peptic ulcers (Gisbert et al., 2004). The accuracy of varying diagnostic test for *H. pylori* in the setting of peptic ulcer bleeding has been studied and suggests an increased false negative rate using any diagnostic method (Barkun et al., 2010; Sanchez-Delgado et al., 2011). *H. pylori* eradication must also be confirmed by subsequent testing.

1.4.7.1.3 General in hospital management:

Most high risk ulcers will take at least 72 hours to become downgraded to low-risk lesions after endoscopic therapy and high dose PPI treatment (Hsu et al., 1994), therefore it is reasonable that patients with high risk stigmata be hospitalized for 72 hours which is also the timeframe within which 80% of cases of further bleeding are likely to occur (Lau et al., 2000; Sung et al., 2009). Patients at low risk of further bleeding can be fed within 24 hours of endoscopy, started on a daily oral dose of PPI, and can be discharged after 1 or 2 days, depending on co-morbid conditions.

1.4.7.2 For AVH

Whilst the same principles of supportive care outlined above apply for patients with AVH, prophylactic antibiotics should be continued for up to 3-5 days post-presentation and vaso-active drugs in combination with endoscopic therapy for up to 3-5 days.

1.5 Outcomes

As for any acute medical emergency, a range of factors can influence reported outcomes of patients with AUGIB, including those related to patients, disease severity and healthcare systems. Outcomes after AUGIB can be categorised as:

- Spontaneous resolution of bleeding, with or without the use of endoscopic therapy, with no episodes of further bleeding.
- Further bleeding which would usually result in repeat endoscopy or other salvage procedures to control bleeding (radiological embolisation, TIPSS procedure or surgery)
- Death directly due to bleeding
- Death from other causes, reflective of the burden of coexistent co-morbidity in many patients with AUGIB.

1.5.1 Spontaneous resolution of bleeding

Bleeding will resolve spontaneously in the vast majority of patients (80%), without the need for endoscopic therapy, as a result of haemostatic and physiological mechanisms in response to bleeding. Prognosis in this group is good with low rates of mortality or further bleeding. In the remaining 20%, endoscopic therapy is needed which is initially effective in more than 90% of patients (Gralnek et al., 2008).

1.5.2 Further bleeding

Case mix will influence rates of further bleeding and it is greatest in those with variceal bleeding and peptic ulcer bleeding with high risk stigmata. Rates of further bleeding provide an assessment of the overall efficacy of all therapeutic interventions – resuscitative, pharmacological and endoscopic - directly targeted at control of

haemorrhage and arguably the best reflection of the effectiveness of care provided to patients with AUGIB. Since mortality rates are 4-5 fold greater in patients who experience further bleeding compared with those who do not, improving outcomes from AUGIB requires a particular focus on the prevention and management of further bleeding.

1.5.3 Mortality

There are several established patient related risk factors for death including older age and concomitant co-morbidities ***(Tables 1.1 and 1.2, p.5).*** Mortality is greatest in patients who suffer with further bleeding, those with cirrhosis and AVH and in patients who develop bleeding whilst hospitalised for another reason. In the majority of cases of AUGIB, death is thought to occur secondary to co-morbid illness, rather than directly due to haemorrhage. NVUGIB is predominantly a disease of older people with 60% of patients above the age of 60 years and 20% above the age of 80 years. Older patients are more likely to have co-morbidity, more likely to use NSAIDS and aspirin and are less physiologically tolerant of major haemodynamic insult.

A study reporting causes of mortality in over 10,000 cases of peptic ulcer bleeding from a single centre in Hong Kong reported that 18% of deaths were related to bleeding and the remainder due to non-bleeding related causes (Sung et al., 2010). The majority of bleeding related deaths occurred when immediate control of bleeding failed, whilst the most common causes of death reported in those who died of non-bleeding related causes were terminal malignancy, respiratory failure and multi-organ failure. Similarly, in patients with liver cirrhosis and AVH, where further bleeding and mortality rates are even greater than those reported in NVUGIB, patients with Child-Pugh C cirrhosis sometimes succumb despite control of haemorrhage (Ben-Ari et al., 1999), since

bleeding can initiate an chain of downstream events resulting in multi-organ failure, independent of adequate control of bleeding (Burroughs and Triantos, 2008).

A review of all deaths (n=675/6750) from the 2007 UK audit of AUGIB using a combination of the primary mode of death as listed on the death certificate as well clinician assessment found that 26% of deaths were related to bleeding. The remainder were not related to bleeding, with the most commonly reported modes of death being respiratory failure, terminal malignancy, sepsis and cardiac failure (Jairath et al., 2010). Other than supportive care, little can be done to correct pre-existing co-morbidity. However, these data indicate that up to one quarter of deaths are deemed to be directly as a result of bleeding, and are therefore potentially preventable. Improving mortality from AUGIB will need to focus upon this latter group of preventable causes of death.

1.6 The need to improve outcomes in the UK

There is widespread variation in reported mortality rates in the literature following AUGIB. This is likely to be influenced by a multitude of factors related to differing study design (source of case ascertainment, inclusion criteria, admission status duration of follow up), patients (case mix, population co-morbidity), healthcare systems (access to emergency endoscopy and surgery) and quality of study reporting (Jairath et al., 2012). These differences can limit the direct comparability of patient related outcomes of mortality and further bleeding.

The large UK audit of AUGIB and the Use of Blood in 2007 collected prospective data on 6750 unselected presentations with AUGIB over an 8 week period in 208 acute care hospitals. In-hospital mortality up to day 28 was 10%, and highest in those with variceal bleeding (15%), with further bleeding rates of 13%. These figures reflect a 30% relative reduction in risk adjusted mortality (adjusted for Rockall score) in comparison to a UK audit conducted in 1993 with similar methodology (where crude mortality was 14% and further bleeding 15%) (Hearnshaw, 2011; Rockall et al., 1995). These reductions in mortality and further bleeding were predominantly noted in the higher risk group of patients with a Rockall score of ≥5 (Hearnshaw et al., 2011). Three UK population based studies using hospital episode statistics (HES) also support this trend of reduced mortality over the past two decades. A HES analysis from Wales found that age and sex adjusted case fatality fell from 11.4% in 1999 to 8.6% in 2007 (Button et al., 2011). Data from Scottish HES found that mortality almost halved for peptic ulcer bleeding between 1982 and 2002 (Kang et al., 2006). Finally, HES data from England reported reductions in overall unadjusted 28 day mortality following hospital admission for both NVUGIB (14.7% to 13.1%) and AVH (24.6% to 20.9%) between 1999 and 2007, although no differences in those aged 80 or more (Crooks et al., 2011).

Whilst these reductions in mortality over time are encouraging, outcomes in the UK are appreciably worse that those reported in large population based studies from other westernised countries. A systematic review of 18 cohort studies including >1000 participants per study originating from 10 countries reported crude case fatality rates in unselected admissions with NVUGIB, and noted widely varying rates ranging from 1.1% to 11.1%, with UK mortality rates amongst the highest at 10% (Jairath et al., 2012). In addition, many other areas of inadequate care for patients with AUGIB were also reported in the UK audit. This work has lead to the development of a toolkit by the UK National Patient Safety Agency to help hospitals improve care of patients with AUGIB, with an associated commentary in the *Lancet* in 2011 (Managing acute upper gastrointestinal bleeding, Lancet, 2011) highlighting these shortcomings in care. Specific shortcomings highlighted include:

1. High mortality and further bleeding rates.
2. The availability of formal out of hours (OOH) provision of emergency endoscopy in only half of UK hospitals with some evidence of an increase in risk adjusted mortality in hospitals without a formal emergency rota (OR 1.25, 95% CI 1.06-1.45).
3. Only 50% of patients receiving endoscopy within 24 hours of presentation (a figure which was identical to the previous audit in 1993).
4. Inadequate use of endoscopic therapy in high risk lesions, with only 74% of such cases receiving any endoscopic therapy and only 38% receiving dual endoscopic therapy, with just 64% of patients with AVH receiving endotherapy.
5. Evidence that 25% of consultants performing emergency endoscopy were not competent at four basic haemostatic procedures.

Altering outcomes from AUGIB in the UK requires identification of processes of care which could be improved in order to have a meaningful impact upon clinical course, as well as identifying which patient groups have the potential to benefit most from these interventions. In the lowest risk group of patients (e.g. Rockall scores <3 or GBS scores <2) it is unlikely that any measureable reduction in case fatality or further bleeding will be achieved through changes in process of care, since the risk of death is very small and in the majority, AUGIB will resolve spontaneously or with simple medical intervention. At the other end of the spectrum, some patients have such severe co-morbidity (e.g. advanced cardiac or respiratory disease, terminal cancer) that prognosis will be determined by their co-morbidity rather than the bleeding, even if bleeding is trivial.

Therefore the group most likely to benefit are the "middle group" who present with significant haemorrhage, haemodynamic compromise and require support and interventions to arrest bleeding - including initial resuscitation, blood components, pharmacological therapy or endoscopic therapy- and to prevent further bleeding. This group represent up to 40% of all patients presenting with AUGIB in the UK, based upon data from the 2007 audit. An especially important subgroup are patients with liver cirrhosis and variceal haemorrhage, since they have the highest further bleeding and mortality rates and are more likely to require the aforementioned interventions due to the nature and severity of bleeding and underlying complex coagulation derangements.

1.7 Aim and outline of thesis

1.7.1 Aim

The aim of this thesis is to investigate how outcomes following AUGIB in the UK could be improved. There are five broad themes tackled in the ensuing chapters which focus upon the potential for improved control of haemorrhage and outcome in patients presenting with AUGIB:

1. **Service provision and timing of endoscopy.** Therapeutic endoscopy is the main factor associated with improvement in outcome over time, therefore earlier access and performance of endoscopy has the potential to better control haemorrhage and influence mortality, further bleeding, use of blood components and length of hospital stay. This is examined in Chapters 3 and 4.

2. **The use of radiological embolisation and surgery for refractory bleeding.** Mortality is greatest in patients where there is primary failure to control bleeding or those who develop further bleeding. Radiological embolisation has the potential to control bleeding as a minimally invasive alternative to major surgery in critically unwell patients after failed endoscopic haemostasis, therefore its use and outcomes are important to characterise in order to better understand its role the current management algorithm of NVUGIB. This is examined in Chapter 5.

3. **The impact of deranged coagulation on outcome in patients with NVUGIB**. Research in other clinical scenarios of major bleeding (e.g. trauma, cardiac surgery) has demonstrated an association between coagulopathy and death, which has lead to major changes in the use of blood components for

resuscitation. Characterising and understanding coagulation derangements after acute presentation may have implications for haemostatic resuscitation to aid primary control of haemorrhage. This is examined in Chapter 6.

4. **Characteristics, management and outcomes of patients with liver cirrhosis and variceal haemorrhage and evaluation of haemostatic abnormalities and response to treatment.** The rising incidence of cirrhosis and variceal haemorrhage in the UK requires a particular focus upon the processes of care in this high risk group. A better understanding and global characterisation of their complex coagulation derangements and response to pro-haemostatic transfusion strategies may help to achieve control of haemorrhage in the acute phase following bleeding and potentially minimise further bleeding. This is examined in Chapters 7 and 8.

5. **Use of RBC transfusion for AUGIB.** As has been observed in other critically ill patients cohorts (intensive care, cardiac surgery), a restrictive approach to RBC transfusion in patients with AUGIB may be associated with more favourable outcomes. Attitudes towards RBC transfusion from a large national survey of multi-disciplinary specialists is reported in Chapter 9. This helped to inform the design and conduct of a national, cluster randomised feasibility trial of restrictive versus liberal blood transfusion strategies which is now complete and is briefly described in Chapter 10.

1.7.2 Outline

1. Materials and methods are discussed in Chapter 2.

2. The primary analyses of the thesis are presented in Chapters 3 to 9. Within each chapter there is a brief introduction and where necessary some additional chapter specific methods, followed by results, discussion and a summary.

3. A summary of the findings and implications of this thesis are presented in Chapter 10. This is followed by a description of further studies that have arisen from this programme of work.

4. References appendices and are presented at the end of the thesis.

2 Chapter Two

Materials and Methods

Data for the primary analyses in Chapters 3-9 arise from three sources:

1. UK national audit of AUGIB and the Use of Blood conducted in 2007. Chapters 3-7 describe a series of secondary analyses derived from this dataset.

2. A laboratory study which was designed to characterise global derangements in coagulation in patient with liver cirrhosis presenting with AVH and the response to pro-haemostatic blood components. This is described in Chapter 8.

3. A cross–sectional study designed to characterise attitudes towards RBC transfusion practice in patients with AUGIB, in order to help inform the design of an RCT of differing blood transfusion strategies in patients with AUGIB. This is described in Chapter 9.

The methodology of the UK national audit of AUGIB and the cross sectional study is described in the sections that follow. The methodology of the laboratory study is described in Chapter 8.

2.1 National Audit of Acute Upper Gastrointestinal Bleeding

2.1.1 Study rationale and methodology

The first large scale observational study of AUGIB in the UK was undertaken in 1993/4 and formed the basis of the 2002 BSG guidelines (Palmer, 2002) and derivation of the Rockall risk score (Rockall et al., 1996). NHS Blood and Transplant had identified AUGIB as a key research area in which to measure the use of RBCs in 2006, and at a similar time, the BSG were also planning to re-evaluate the provision of services to and outcomes of patients with AUGIB since the last study in 1993. This lead to collaboration between NHSBT and the BSG in 2007 and the audit was conducted as part of the UK National Comparative Audit Programme. Although the study methodology has been previously described (Hearnshaw, 2011), it is summarised below with an additional focus on the completeness of case ascertainment.

All NHS trusts in England, Scotland, Wales and Northern Ireland accepting acute admissions were invited to take part in the study. Participating sites were required to identify all new presentations with all-cause AUGIB over a two month period between May 1st – June 20th in 2007, including new presentations to hospital with AUGIB as well as those who developed bleeding whilst already hospitalised for a another condition. Of the 257 NHS trusts invited, 223 (87%) agreed to take part and 217 (84%) submitted data. Participation was voluntary and reliant largely upon goodwill of local clinicians with variable support from hospital audit departments.

Patients were eligible if they were aged 16 years or over, presenting with clinical evidence of AUGIB defined by haematemesis (vomiting blood, blood clots or "coffee grounds" witnessed by nursing or medical staff) or melaena (passage of dark tarry stool or altered blood as witnessed by nursing/medical staff, or discovered on rectal

examination). A pilot phase was conducted in six UK hospitals in order to refine the methodology of case ascertainment and data collection. Patients were identified daily from acute admission units, endoscopy departments, blood transfusion laboratories, direct contact with wards and through staff posters.

Demographic data, clinical findings, laboratory results, endoscopy results, fluid and blood component transfusion, use of endoscopic therapy, radiological intervention and surgery were recorded for each patient. Outcomes included all cause mortality (in-hospital), further bleeding, the need for rescue treatments to control bleeding (radiological intervention, surgery) and duration of hospital stay.

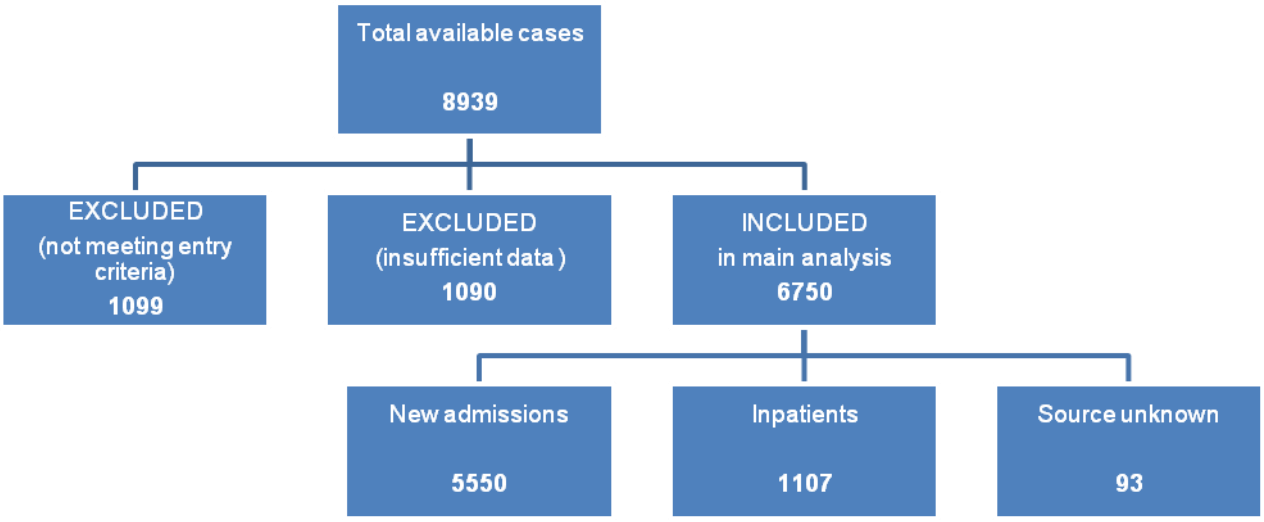
2.1.2 Data entry and handling

All data were entered electronically by case ascertainers at hospital sites onto the National Comparative Audit of Blood Transfusion (NCABT) website. A minimum data-set was required in order to submit each case record. These data were exported into Microsoft Excel and exported into SPSS by the Royal College of Physicians Clinical Evaluation and Effectiveness Unit (CEEU) statistician. The central team excluded cases not meeting the entry criteria and removed any duplicate cases.

In total 8939 cases of AUGIB were identified and registered submitted by 208 UK hospitals over an 8 week period. This data-set includes detailed information on over 1000 variables related to AUGIB and the use of blood components, both in patients with NVUGIB and in patients with liver cirrhosis and AVH. 13% (1099/8939) of these cases were excluded by local hospital leads as they were deemed not to have met entry criteria. A further 12% (1090/8939) were excluded by the audit team due to incomplete data – in 890 there was insufficient data to confirm an AUGIB and in a further 200 only

minimum data were submitted ***(Figure 2.1).*** The most common reasons provided by hospitals were time pressure and loss of case records and. In total, 6750 cases from 208 hospitals were included in the final data-set. There was no difference in terms of age (68 vs. 71 years) and gender (59% vs. 55% male) between included cases (n-6750) and those excluded (n=1090) due to insufficient data.

Figure 2.1: Flow chart of case ascertainment



2.1.2.1 Missing data

In the final data-set, the admission status for 93 (1.4%) patients was unknown. No medication record was available in 58/1107 (5.2%) of hospitalised patients and in 285/5550 (5.1%) of new presentations. Of the 5004 patients who underwent endoscopy, there was no record of the endoscopic finding in 15 (0.3%) patients.

In the analyses presented in Chapters 3-7, a variable, but small proportion of data were incomplete for some of the variables used in logistic regression models. It is reasonable to make the assumption that these data were missing at random (MAR), as opposed to missing not at random (MNAR) (Rubin, 1976), since the reasons for missing data were related to time pressure and resources required in case identification and entry, as opposed to specific patient characteristics or outcomes which may have influenced case ascertainment and data entry. A number of strategies are available to deal with these missing data:

1. Complete case analysis only i.e. analyse those participants who have no missing values; in general this approach will lead to biased estimates as well as loss of efficiency.
2. Analyse all available data, which is generally preferable to analysis of complete cases, provided appropriate analysis techniques are used.
3. To use multiple imputation. This is a technique which accounts for the uncertainty caused by missing data and provides more reliable results than complete case capture in most situations (Royston, 2007). It involves replacing missing values with predictions from a statistical model. A set of plausible values for missing observations are created and each of these sets is then used to fill in missing values and create a "completed" dataset; each of these sets is analysed and the results combined to take into account imprecision in parameter

estimates from each "completed" dataset and the variation between data-sets (Barzi and Woodward, 2004). Unless stated otherwise, multiple imputation was used in each logistic regression analysis in Chapters 3-7 to account for any missing data, thereby permitting all cases to be analysed.

2.1.2.2 Case ascertainment and comparison with Hospital Episode Statistics

Complete case capture was not achieved in all sites. This was apparent become some larger sites only submitted a small number of cases. To explore the impact that lack of case ascertainment may have had on the conclusions of the original audit, the study team recalculated mortality after removing data from those hospitals submitting the smallest number of cases. Crude case fatality using all data from all hospitals was 10%. Removal in turn of the lowest 5%, 10% then 25% of the 208 hospitals submitting the least number of cases resulted in no change in the crude mortality (9.98% vs. 10% vs. 9.95% respectively) or Rockall adjusted mortality (OR= 0.91, 95% CI 0.78-1.03; OR=0.93, 95% CI 0.86-1.00; OR=0.95, 95% CI 0.88-1.02 respectively; reference OR 1.0 for all included cases) (Hearnshaw, 2011). This consistency after removal of hospitals for both the crude and adjusted mortality rates suggests that the case capture was representative.

More reassuring data was provided by a study comparing results from this audit with data from Hospital Episode Statistics (HES) (Crooks CJ, 2011). Using HES data linked to the Office for National Statistics (ONS), Crooks *et al.* selected records with provider codes that matched the English hospitals which participated in the audit between 1st May and 31st June 2007 and compared number of admissions, deaths and endoscopies between the two studies. The audit contained 7535 records of admissions with AUGIB to English hospitals and HES data recorded 8432 admissions during the same time period, suggesting that the audit captured 90.3% of cases (Crooks CJ, 2011). The audit

recorded 5426 acute admissions with AUGIB, whereas HES data was only able to capture 5113 (94%) of these. The use of endoscopy was recorded in 55.8% of cases in the audit, whereas HES was only able to capture its use in 46.6% of cases, with similar trends seen for the use of therapeutic endoscopy and surgery, although slightly more deaths were noted using the ONS figures (10.7%)) compared to the national audit (8.3%). There are strengths and weaknesses using data from large nationwide audits versus HES derived data. However these results provide re-assurance that both methods were sufficiently robust in terms of case ascertainment for cases of AUGIB between May 1st-June31st in 2007, providing further re-assurance that the results of the audit were broadly representative of all UK hospitals at the time.

2.1.3 Ethical approval

A programme of National Comparative Audits of Blood Transfusion (http://hospital.blood.co.uk/safe_use/clinical_audit/National_Comparative/index.asp) is carried out as collaboration between NHSBT and the Royal College of Physicians Clinical Effectiveness Unit to assess if healthcare professionals are conducting blood transfusion in accordance with best practice. The audit of AUGIB in 2007 was observational and the data collected constitute information that should be routinely recorded in medical records. There was no patient intervention and no patient outcome was influenced by the audit. The need for patient consent was removed by the *NHS Code of Practice* (2003), which allows for information relating to a patient to be used for clinical audit purposes, but in the main addresses the issue of patient identifiable data. National Comparative Audits do not collect patient identifiable data. Therefore no ethical approval was required.

2.2 National survey of Red Blood Cell transfusion practice for Acute Upper Gastrointestinal Bleeding

This national cross-sectional survey was designed to gauge attitudes to transfusion practice amongst a broad group of clinicians who may be involved in the care of patients with AUGIB.

2.2.1 Methodology of Survey Design:

A series of clinical scenarios were developed in conjunction with clinical experts, representing a spectrum of typical cases of AUGIB. Each vignette began with a patient history and clinical examination, followed by a range of Hb triggers for RBC transfusion (ranging from 4.1-12 g/dL). Respondents were required to select a Hb trigger at which they would ordinarily prescribe a RBC transfusion. There were sufficient data provided in each scenario to calculate a clinical Rockall Score, although this value was not explicit in the text. Two of the six scenarios then gave a range of consistent endoscopic diagnoses, each with a differing risk of re-bleeding, to examine the influence that this had on the transfusion trigger. The questionnaire layout included both vertical single best answers, horizontal matrix items and an opportunity for free text and comments with each response. Clinician characteristics (year of graduation, gender, primary specialty, type of hospital practice and knowledge of national guidelines of AUGIB) were recorded.

2.2.2 Selection of participants:

Responses from consultants and trainees in gastroenterology, acute medicine and upper gastrointestinal surgery were sought through their representative organizations (BSG, 1288 total members, 580 members relevant to this survey). Trainees in

Gastroenterology (TIG, 574 members), the Society for Acute Medicine (SAM, 316 consultants and 404 trainees) and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS, 417 relevant members to this survey)). Lists were manually searched to select consultants in clinical practice, followed by an on-line search of each individual hospital to confirm they were currently practicing. Systematic random sampling selected every second name in an alphabetical list. SAM and AUGIS preferred to email the survey directly to its members, excluding overseas and retired members.

2.2.3 Pilot Study:

The survey was piloted (November 2009) among consultants and trainees in gastroenterology, from district general and university teaching hospitals. 42/75 (56%) responded, which led to minor modifications in terminology, but no substantive changes that would have necessitated re-piloting.

2.2.4 Survey Distribution:

The questionnaire was distributed via an online platform (www.surveymonkey.com) in December 2009. Each participating organisation had a unique link for their members, with an explanatory paragraph and a link for the survey. A follow up email was sent to encourage non-responders after 2-3 weeks in accordance with the principles outlined by Dilman (Dillman, 1978). Participation was voluntary. All recipients could opt out of the survey and reminder emails.

3 Chapter Three

Weekend versus weekday mortality following Acute Upper Gastrointestinal Bleeding

3.1 Introduction

AUGIB is an ideal condition to examine for the presence of a "weekend effect". It is a common medical emergency and carries significant morbidity and mortality. There are several processes involved in the management of patients with AUGIB including prompt resuscitation, risk stratification, triage and access to early endoscopy performed by operators skilled in all aspects of endoscopic haemostasis. Some of the steps in these processes may be less available at weekends, particularly access to early endoscopy. Indeed, the 2007 audit of AUGIB in the UK found a number of deficiencies in the provision and use of endoscopy for AUGIB; only 52% of hospitals had a formal out of hours endoscopy rota and only 50% of admissions with AUGIB received endoscopy within 24 hours of presentation (Hearnshaw et al., 2010).

3.2 Aims

Given some of the reported deficiencies highlighted in the 2007 UK national audit, this analysis was performed with the following objectives:

1. To determine if weekend presentations with AUGIB in the UK have a higher mortality compared to patients admitted on weekdays.
2. To analyse differences in weekend versus weekday mortality between hospitals with an out of hours endoscopy facility compared to hospitals without such a facility.

3. To examine differences in weekend versus weekday mortality in patients presenting with variceal bleeding compared to those presenting without variceal bleeding.
4. To explore differences in receipt of therapeutic endoscopy, length of hospital stay (LOS) and RBC transfusion between weekend and weekday presentations with AUGIB.

3.3 Methods

3.3.1 Definition of weekend

Previous studies examining for the possibility of a weekend effect following AUGIB have defined the weekend as presentation between midnight on Friday through to midnight on Sunday (Ananthakrishnan et al., 2009; Shaheen et al., 2009). These studies have used administrative databases which are unlikely to give details of specific time of presentation. In order to aid comparability with these studies, weekend was primarily defined as midnight on Friday through to midnight on Sunday. However, it is possible that results could be influenced according to the definition of a weekend. For example, it is possible that the reduced staffing pattern seen at weekends may actually begin at the end of duty hours on a Friday, rather than from midnight on Friday. Similarly, patients presenting on Sunday after 5pm may be more likely to get an early endoscopy than patients presenting earlier in the weekend. In order to test whether results were sensitive to the definition used for a weekend, three sensitivity analyses were performed; the first defining weekend as 5pm Friday-midnight Sunday, the second defining weekend as midnight Friday-5pm Sunday, and the third defining weekend as 5pm Friday-5pm Sunday.

3.3.2 Statistical methods

A logistic regression model was used to examine the relationship between weekend presentation to hospital and mortality. Both unadjusted and adjusted analyses were performed. The adjusted model included 15 pre-specified variables that were possible predictors of outcome, selected from a list of variables based on clinical relevance among baseline clinical characteristics, endoscopic findings, pharmacological therapies and admission status. These variables included: the individual components of the clinical Rockall score (age, presentation with shock, co-morbid illnesses), presentation with haematemesis, presentation with melaena, Hb and urea concentration on admission, use of aspirin, use of NSAIDS, use of PPIs, gender, variceal bleeding, peptic ulcer bleeding, whether or not an out-of-hours rota enabling 24-hour access to endoscopy was available at the admitting hospital and admission status (new admission versus in-patient).

3.3.3 Outcome measures

Analyses for the primary outcome of mortality were performed *initially* for all patients presenting with AUGIB and *then for only* those patients who underwent endoscopy during their hospital admission, as this represents a higher risk group of patients who specifically require intervention to control bleeding and may be most affected in there is a "weekend effect". Pre- specified subgroup analyses were:

1. New admissions versus existing in-patients who developed AUGIB.
2. Variceal versus non-variceal bleeding.
3. Peptic ulcer versus non-peptic ulcer bleeding.
4. Hospitals with a formal out of hours endoscopy rota versus those without such a rota.

Secondary outcomes included further bleeding, receipt of RBC transfusion, receipt of therapeutic endoscopy, surgical or radiological intervention to control bleeding, length of hospital stay and time to endoscopy. All secondary analyses were adjusted for the same variables as the primary analysis.

3.4 Results

Of the 6,750 patients in the dataset, the day of presentation was missing in one patient leaving 6,749 patients for this analysis of whom 5004 underwent endoscopy (74%).

3.4.1 Patient characteristics

The demographic and clinical characteristics of patients presenting at the weekend with AUGIB compared to weekday are summarised in ***Table 3.1***. There were small differences in baseline characteristics between patients admitted at weekdays versus weekends; a greater proportion of patients presenting at the weekend were shocked (39% vs. 36%, p=0.03) and presented with haematemesis (41% vs. 38%, p=0.03), and a smaller proportion presented with melaena (46% vs. 50%, p=0.003). A similar pattern was seen when restricting the analysis to those patients whom underwent endoscopy ***(Table 3.1).***

Table 3.1: Clinical characteristics of patients presenting on the weekend versus weekday

Variable	All Patients n= 6,749			Patients Undergoing Endoscopy n=5004		
	Weekday n=5250 % (n)	Weekend n=1499 % (n)	*p* value	Weekday n=3931 % (n)	Weekend n=1073 % (n)	*p* value
New admission	84 (4321)	83 (1228)	0.73	83 (3232)	83 (877)	0.72
Age years mean (SD)	64.4 (19.7)	64.2 (19.8)	0.64	65.2 (18.4)	64.8 (18.3)	0.98
Male	59 (3106)	60 (902)	0.49	60 (2374)	62 (666)	0.33
Presenting signs/symptoms						
Shock	36 (1851)	39 (575)	0.03	38 (1466)	41 (429)	0.11
Haematemesis	38 (1969)	41 (608)	0.03	36 (1429)	40 (432)	0.003
Melaena	50 (2632)	46 (687)	0.003	56 (2197)	54 (578)	0.24
Clinical Rockall Score (mean, SD)	2.59 (1.87)	2.60 (1.86)	0.83	2.65 (1.80)	2.65 (1.79)	0.98
First recorded laboratory results						
Haemoglobin g/dl mean (SD)	10.9 (3.2)	11.1 (3.3)	0.07	10.5 (3.2)	10.5 (3.2)	0.56
Urea median (IQR)	10.9 (5-14)	11.5 (5-15)	0.23	11.5 (5 -15)	12.4 (6-15)	0.17
Out of hours facilities						
Presentation to hospital with out of hours Endoscopy rota	56 (2739)	54 (759)	0.31	57 (2739)	58 (590)	<0.01
Medication						
Aspirin	30 (1470)	29 (404)	0.43	32 (1172)	30 (307)	0.45
NSAID	12 (576)	13 (175)	0.46	13 (464)	14 (139)	0.32
PPI	31 (1517)	30 (410)	0.26	30 (1125)	29 (291)	0.34
Endoscopic diagnosis	-	-	-			
Peptic ulcer				35 (1367)	35 (378)	0.80
Varices				12 (464)	13 (137)	0.40

3.4.2 Mortality for all patients

There was no difference in the unadjusted mortality between patients presenting at the weekend compared to weekdays (crude mortality 10% vs. 10% respectively, OR 0.98; 95% CI 0.81-1.19, p=0.83) ***(Tables 3.2 and 3.3).*** Similarly, after adjusting the individual components of the clinical Rockall score (age, presentation with shock, co-morbid illnesses), presentation with haematemesis, presentation with melaena, Hb and urea concentration on admission, use of aspirin, use of NSAIDS, use of PPIs, gender, variceal bleeding, peptic ulcer bleeding, whether or not an out-of-hours rota enabling 24-hour access to endoscopy was available at the admitting hospital and admission status (new admission versus in-patient), there was no evidence of increased mortality for patients presenting at the weekend (OR= 0.93 ; 95% CI 0.75 to 1.16, p=0.52) ***(Table 3.3).*** All sensitivity analyses showed similar results (weekend defined as 5pm Friday-5pm Sunday; OR=1.01, 95% CI 0.82 to 1.25, p=0.92).

3.4.3 Mortality for patients undergoing endoscopy

Unadjusted mortality for patients presenting at the weekend compared to weekdays was similar (crude mortality 7% vs. 8%, OR 0.91; 95% CI 0.69-1.18, p=0.47). After adjustment the OR for mortality for weekend versus weekday presentation was 0.87 (95% CI 0.65 to 1.16, p=0.35) ***(Tables 3.2 and 3.3).*** All sensitivity analyses showed similar results (including the weekend defined as 5pm Friday-5pm Sunday; OR=0.99, 95% CI 0.75 to 1.32, p=0.97).

Table 3.2: Unadjusted clinical outcomes for all patients presenting with AUGIB on the weekend versus weekday

Variable	**All Patients n= 6,749**			**Patients Undergoing Endoscopy n=5004**		
	Weekday (n=5250) **%** (n)	**Weekend (n=1499)** **%** (n)	**Overall**	**Weekday (n=3931)** **%** (n)	**Weekend (n=1073)** **%** (n)	**Overall**
Mortality	10 (527)	10 (148)	10 (675)	8 (297)	7 (74)	7 (371)
Further bleeding	13 (529)	13 (139)	13 (668)	13 (529)	13 (139)	13 (668)
Surgery/radiology	3 (49)	3 (152)	3 (201)	3 (134)	4 (43)	4 (177)
Therapeutic endoscopy	17 (917)	17 (255)	17 (1172)	24 (917)	24 (255)	24 (1172)
RBC Transfusion	33 (1737)	34 (504)	33 (2241)	39 (1527)	42 (447)	39 (1974)

Table 3.3: Odds Ratios for outcomes of weekend versus weekday presentation with AUGIB for all patients

Variable	Unadjusted OR, 95% CI			Adjusted OR, 95% CI*		
All Patients	**OR****	**95% CI**	**p**	**OR**	**95% CI**	**p**
Mortality	0.98	0.81 to 1.19	0.83	0.93	0.75 to 1.16	0.52
Further bleeding	0.94	0.77 to 1.16	0.58	0.91	0.74 to 1.11	0.35
Surgery/radiology	1.13	0.82 to 1.57	0.46	1.13	0.81 to 1.59	0.46
RBC transfusion	1.03	0.90-1.16	0.70	1.12	0.94-1.33	0.22
Patients Endoscoped	**OR****	**95% CI**	**p**	**OR**	**95% CI**	**p**
Mortality	0.91	0.69 to 1.18	0.47	0.87	0.65 to 1.16	0.35
Re-Bleeding	0.94	0.77 to 1.16	0.58	0.89	0.72 to 1.11	0.29
Surgery/radiology	1.18	0.83 to 1.68	0.35	1.15	0.80 to 1.65	0.45
Therapeutic endoscopy	1.00	0.85 to 1.18	0.99	0.94	0.78 to 1.14	0.53
Endoscopy within 24 hours	0.47	0.41 to 0.55	<0.001	0.47	0.41 to 0.54	<0.001
RBC transfusion	1.12	0.97 to 1.28	0.12	1.21	0.99 to 1.48	0.06

*Model adjusted for the individual components of the clinical Rockall score (age, presentation with shock, co-morbid illnesses), presentation with haematemesis, presentation with melaena, Hb and urea concentration on admission, use of aspirin, use of NSAIDS, use of PPIs, gender, variceal bleeding, peptic ulcer bleeding , whether or not an out-of-hours rota enabling 24-hour access to endoscopy was available at the admitting hospital and admission status (new admission versus in-patient)

**Reference category weekday OR = 1.0

3.4.4 Further bleeding and Receipt of RBC Transfusion

The proportion of patients who suffered from further bleeding ***(Tables 3.2 and 3.3)*** was comparable between weekend and weekday presentation (13% vs. 13% respectively, adjusted OR in those undergoing endoscopy 0.89; 95% CI 0.72-1.11, p=0.29). There was some evidence that patients presenting at weekends were more likely to receive RBC transfusion compared to those presenting on weekdays, and this was the case for all patients (34% vs. 33% respectively, adjusted OR 1.12, 95% CI 0.94-1.33, p=0.22) as well as just those patients who underwent endoscopy, (42% vs. 39% respectively, adjusted OR 1.21, 95% CI 0.99-1.48, p=0.06) ***(Tables 3.2 and 3.3).***

3.4.5 Therapeutic endoscopy and Surgical/Radiological Intervention

Overall receipt of therapeutic endoscopy was identical for weekend and weekday presentations (24% vs. 24% respectively, adjusted OR 0.94; 95% CI 0.78-1.14, p=0.53). In those patients endoscoped there was also no difference in need for surgery and/or radiological intervention to control bleeding on weekends versus weekdays (4% vs. 3% respectively, adjusted OR 1.15; 95% CI 0.80-1.65, p=0.45) ***(Tables 3.2 and 3.3).***

3.4.6 Time to Endoscopy and Length of Hospital stay

Only 38% of those presenting at weekends underwent endoscopy within 24 hours compared to 55% admitted on weekdays (adjusted OR 0.47, 95% CI 0.41-0.54, p<0.001). The median time from presentation with AUGIB to endoscopy was 21.8 hours (IQR 11.3-47.7) for weekday presentation and 38.9 hours (IRQ 15.8-64.2) for weekend presentation. There was no evidence of a difference in the LOS between patients presenting at the weekend or weekdays. For all patients the mean adjusted LOS was 0.20 days longer (95% CI -0.90-1.30, p=0.72) for patients presenting at the

weekend compared to the weekday and similarly in those undergoing endoscopy the mean adjusted LOS was just 0.27 days longer (95% CI, -0.88-1.42, p=0.65) for those presenting at weekends compared to weekday ***(Tables 3.2 and 3.3).***

3.4.7 Subgroup analyses for Mortality

There was no evidence that the OR for mortality at weekends compared to weekdays was different for new admissions compared to in-patients (OR for in-patients =0.85, OR for new admission =0.98; p=0.56). Similarly, there was no evidence of a difference in odds ratio for mortality between patients presenting to a hospital with an out-of-hours (OOH) endoscopy rota compared to a hospital with no OOH endoscopy rota (OR for hospitals with OOH rota = 0.86, OR for hospitals with no OOH rota =1.02; p=0.44). For patients who underwent endoscopy, there was no evidence that the OR for mortality for weekend presentation compared to weekday was different for variceal bleeding versus non-variceal bleeding patients (OR for variceal bleeding =1.03, OR for non-variceal bleeding =0.83; p=0.55), or between peptic ulcer versus non-peptic ulcer bleeding patients (OR for peptic ulcer bleeding =0.83, OR for non-peptic ulcer bleeding=0.90; p=0.80) ***(Table 3.3).***

3.5 Discussion

This analysis is based on the largest ever UK national audit of AUGIB with over 75% of acute hospitals providing comprehensive and "real-life" outcome data from a large number of prospectively identified cases, enabling adjustment for key disease specific prognostic and confounding variables. Key findings from this analysis were:

1. Patients presenting at weekends were more likely to present with shock and haematemesis and to receive blood transfusion compared to weekday presentations.
2. There was no difference in the risk adjusted mortality of patients presenting with AUGIB at weekends compared with weekdays;
3. There was no difference in weekend versus weekday mortality in those patients presenting to hospitals with an out of hours endoscopy rota compared to those without such a rota.
4. There was no difference in weekend versus weekday mortality between patients presenting with variceal bleeding, compared to those with non-variceal bleeding;
5. There was no difference in receipt of therapeutic endoscopy or LOS between weekend and weekday presentation.
6. There were significant delays to endoscopy in those patients who presented on weekends with only 38% receiving endoscopy within 24 hours of presentation. Despite this there was no overall evidence of a "weekend effect" after adjustment for confounding and disease specific prognostic variables.

The absence of a "weekend effect" for AUGIB is supported by data from some previous studies. Bell and Redelmeier found no difference in mortality in a large Canadian cohort of 30,129 patients with gastrointestinal haemorrhage (OR 1.08; 95% CI 0.96-1.20), nor

in a sub-group of patients presenting with duodenal ulcers on the weekend (OR 0.98, 95% CI 0.82-1.17) (Bell and Redelmeier, 2001). Two smaller studies from Europe also failed to detect a weekend effect for mortality, although their size may have limited the ability to detect such a difference (Schmulewitz et al., 2005) (Nahon et al., 2009). A large study from Hong Kong reported the risk of ulcer related death in a cohort of 10,428 cases of peptic ulcer bleeding in relation to public holidays and found no evidence of increased mortality on public holidays compared to normal working days (Tsoi et al., 2010).

The findings of this study are not in agreement with those of two recent large US studies, which found that mortality was about 10-20% higher in patients admitted at weekends compared to weekdays (Ananthakrishnan et al., 2009; Shaheen et al., 2009). There are several possible reasons which might account for why our findings differ. Both US studies utilized discharge data from the US Nationwide Inpatient Sample, representing a 20% stratified sample of non-federal acute-care hospitals and the samples included non-emergency admissions, which predictably had a lower mortality and were more likely to occur during the week (Ananthakrishnan et al., 2009). Secondly, through the use of a large administrative database, both US studies were reliant on ICD-9-CM discharge coding; although powerful in their scope and size, they were unable to adjust for several well defined prognostic factors in AUGIB including clinical features of shock and biochemistry (urea, Hb) which may have resulted in unrecognized confounding (Barkun, 2009). Thirdly, there is the possibility that there is greater variation in delivery of healthcare across the US than there is in the UK. A fourth possibility is that the sample size of the present study has not been sufficient to detect the small differences in weekend versus weekday mortality found in the large US studies, if indeed the differences they found are real (a type 2 error). However, this is

unlikely since the sample size was sufficiently large (6,749 patients) to obtain a precise estimate of the difference in weekend mortality. In addition patients presenting on the weekend actually had a slightly lower risk of mortality (OR=0.93), making it unlikely that the difference between studies was solely due to a difference in sample size.

Given some of the deficiencies in the use of endoscopy for AUGIB in the UK, which have been recently highlighted, the lack of a weekend effect for mortality is perhaps surprising (Hearnshaw et al., 2010). It may indicate that those critically ill patients who are most likely to benefit from early endoscopy do actually receive one at weekends, whether or not a hospital has a formal OOH endoscopy rota. Some evidence for this is that, in hospitals without an OOH rota, 13% of endoscopies for AUGIB were performed OOH which was only a little less than the 20% performed OOH in hospitals with a formal OOH rota (Hearnshaw et al., 2010). Furthermore, the proportion of all patients who received endoscopic therapy was identical at weekends compared to weekdays and this equivalent use of therapeutic intervention may contribute to the lack of a weekend effect. The absence of a weekend effect may also reflect deficiencies in the weekday management of AUGIB. Notably only 55% of patients presenting on a weekday underwent endoscopy within 24 hours of presentation and deficiencies have been reported in the use of therapeutic endoscopy for lesions with high risk stigmata (Hearnshaw et al., 2010). In particular only 64% of patients presenting with variceal bleeding received therapeutic endoscopy.

Previous studies have suggested that those patients presenting at weekends may be more critically ill than those presenting on weekdays and postulate that patients admitted to hospital on the weekend may present later in their disease course. The present analysis supports this observation; a greater proportion of patients presenting at the weekend

were shocked, presented with haematemesis and received blood transfusion, although transfusion may not be a reliable surrogate marker of disease severity given the wide variation in RBC transfusion practice found in this audit and in another recent UK study (Stanley et al., 2010). However even after adjustment for factors associated with severity of disease presentation we still found no evidence of a weekend effect for mortality.

The most notable characteristic of patients presenting at weekends was the significant delay in time to endoscopy compared to weekday presentations. Coupled with the observation that more critically ill patients presented at weekends, it is surprising that this did not result in increased mortality for weekend presentations. However the impact of early endoscopy on mortality has been debated since the advent of therapeutic endoscopy and no study has yet been able to clearly demonstrate that early endoscopy results in a reduction in mortality. There are clearly other important processes and aspects in the quality of care in patients with AUGIB, often unmeasurable, with some evidence to point towards benefits of early endoscopy in other clinically important outcomes including further bleeding, need for emergency surgery, transfusion and length of hospital stay. Furthermore, prompt resuscitation and stabilisation of patients prior to endoscopy is the most important aspect of initial care and it is likely that this aspect of emergency care is no different at weekends compared to weekdays, regardless of the availability of OOH endoscopy facilities.

3.6 Summary

Patients presenting at weekends are more critically ill and have greater delays to the performance of endoscopy. Despite this, there was no difference in the risk adjusted mortality for patients presenting at weekends compared to weekdays, regardless of whether or not a hospital had a formal out of hours endoscopy service. Provision of an OOH endoscopy service at weekends in the remainder of UK hospitals may not lead to further reductions in case fatality from AUGIB. However, given the proportion of patients receiving endoscopic intervention is currently identical between weekend and weekday presentations, it is conceivable that any reduction in out of hours endoscopy service provision from current levels could lead to an increase in mortality in weekend presentations.

4 Chapter Four

Outcomes following acute non-variceal upper gastrointestinal bleeding in relation to time to endoscopy

4.1 Introduction

To date, only one recent single-centred retrospective observational study has been able to demonstrate an association between earlier endoscopy and a reduction in mortality in higher risk patients (Lim et al., 2011). Non-randomised studies have produced conflicting results with some demonstrating lower further bleeding rates and need for surgery through earlier endoscopy (Cooper et al., 2009; Cooper et al., 1999), with others suggesting either no clinical benefit or even an increased risk of complications associated with earlier endoscopy (Choudari CP, 1993; Yen et al., 1997). A systematic review in 2001 examined the impact of time to endoscopy in NVUGIB, which included four small randomised controlled trials (RCTs), none of which were able to demonstrate any improvement in clinical outcomes through early endoscopy (Spiegel et al., 2001).

In the absence of randomised studies of sufficient power to address this question, this study reports the results of the largest observational study so far to have examined the relationship between time to endoscopy and clinically important outcomes following admission to hospital with NVUGIB.

4.2 Aims

To examine the relationship between time to endoscopy and clinically important outcomes following admission to hospital with NVUGIB. Specific aims were to determine if in patients presenting with NVUGIB, earlier versus later endoscopy led to a reduction in the following parameters:

1. Mortality.
2. Further bleeding.
3. Need for surgery and/or radiological intervention.
4. RBC transfusion.
5. Length of hospital stay.

4.3 Methods

4.3.1 Definition of time-to-endoscopy

Time to endoscopy was defined as the delay (in hours and minutes) between presentation with symptoms of AUGIB and performance of the index endoscopy.

4.3.2 Statistical methods

Patients undergoing earlier endoscopy are likely to be more critically unwell than those patients undergoing later endoscopy. In order to make a meaningful comparison of outcomes in those undergoing earlier versus those undergoing later endoscopy, adjustment for markers of disease severity are necessary in order to account for potential confounding. Therefore a logistic regression model was used to examine the relationship between time-to-endoscopy and mortality (Rabe-Hesketh S, 2008).

The adjusted model included a pre-specified set of potential confounding variables that were possible predictors of outcome, selected from a list of variables based on clinical relevance among baseline clinical characteristics, endoscopic findings, pharmacological therapies and admission status. These variables were: age, presentation with shock, co-morbid illnesses (ischaemic heart disease, heart failure, respiratory disease, cancer, stroke, dementia, cirrhosis and renal failure), presentation with frank haematemesis or melaena, Hb and urea concentration on admission, a prolonged coagulation screen on

admission, NSAIDS, warfarin, or PPIs, severity of endoscopic stigmata and admission status (new admission versus in-patient). Only those patients who underwent endoscopy during this admission and were confirmed to have a non-variceal source of haemorrhage were included and this was decided *a priori*.

Time-to-endoscopy is a continuous variable, but in previous analyses of the impact of time to endoscopy and outcome, it has been categorised (Cooper et al., 1999). Dichotomising a continuous variable can lead to loss of analytical power and precision (Royston et al., 2006). A alternative method to analyse continuous variables is to use fractional polynomials (Royston and Sauerbrei, 2008), which model the relationship between the continuous variable and outcome, even when the relationship is non-linear. In comparison with dichotomised analyses using fractional polynomials increases the power and precision of estimates of association.

Odds ratios for mortality were calculated for time-to-endoscopy <12 hours, 12 to 24 hours, and >24 hours. This was performed by calculating the increase in odds between the median time-to-endoscopy values in each category from the fractional polynomial model. For example, if the median time-to-endoscopy was 6 hours in the <12 hours group, and 17 hours in the 12-24 hours group, the odds ratio for mortality for the 12-24 hours group compared to the <12 hour group would be the increase in odds going from a time-to-endoscopy of 6 hours to 17 hours. In this way the continuous nature of the variable was maintained.

Timing of endoscopy is most likely to be dictated by local resource. However to assess for the possibility of "tie-breaker bias" around 24 hours a sensitivity analysis was performed to assess the period effect for mortality by comparing 12-22 hours with >26 hours.

4.3.3 Outcome measures

Secondary outcomes included the impact of time-to-endoscopy on further bleeding, receipt of RBC transfusion, need for surgical or radiological intervention to control bleeding, and LOS. A pre-specified subgroup analysis examined whether the effect of earlier (<12 hrs or 12-24 hours) versus later endoscopy (> 24 hours) differed between patients who received a therapeutic intervention at endoscopy compared to those who did not and performed for each outcome using an interaction test.

4.4 Results

Of the 6750 cases in the dataset, 5004 underwent an in-patient endoscopy. A total of 526 patients had liver cirrhosis and AVH and were excluded from the analysis, leaving 4478 cases of endoscopically confirmed NVUGIB. Data for time to index endoscopy was not available in 296 cases, which was accounted for by multiple imputation.

4.4.1 Patient characteristics and endoscopic stigmata

Baseline clinical characteristics and endoscopic stigmata stratified by time to endoscopy are summarised in ***Table 4.1*** (<12 hours, 12-24 hours and >24 hours). The median time to endoscopy was 24.6 hours (IQR 14.5 to 54.8). 20% of patients underwent endoscopy within 12 hours of presentation with NVUGIB, 28% within 12-24 hours and 52% after 24 hours. Patients endoscoped within 12 hours were more likely to be shocked, present with haematemesis, have a Rockall score ≥3 and have a prolonged coagulation time. At endoscopy, patients endoscoped within 12 hours were more likely to have high risk stigmata than patients endoscoped between 12-24 hours, or after 24 hours (45.8% versus 26.1% versus 15.8% respectively) and also more likely to receive therapeutic endoscopy than those patients endoscoped between 12-24 hours and after 24 hours (34.1% versus 19.8% versus 11.9% respectively) ***(Table 4.1).***

Table 4.1: Baseline Clinical Characteristics and endoscopic stigmata

	Time to endoscopy <12 hours (n=834, 20%)	Time to endoscopy 12-24 hours (n=1190, 28%)	Time to endoscopy >24 hours (n=2158, 52%)	Proportion of patients with missing data **
Baseline characteristics				
Age (mean, SD)	65.2 (18.4)	64.6 (18.6)	67.6 (18.3)	0 (0)
Gender (male)	529 (63.5)	710 (59.7)	1270 (58.9)	2 (0)
New admission	655 (79.2)	1057 (89.4)	1792 (84.4)	57 (1.3)
Disease presentation				
Shock	382 (46.4)	437 (37.2)	669 (31.7)	80 (1.8)
Haematemesis	344 (41.2)	425 (35.7)	615 (28.5)	3 (0.1)
Melaena	476 (57.1)	714 (60.0)	1174 (54.5)	3 (0.1)
Clinical Rockall score ≥3 (high risk)	305 (36.6)	362 (30.4)	729 (33.8)	0 (0)
Drug History				
Aspirin	286 (35.9)	376 (32.8)	693 (33.9)	228 (5.1)
NSAIDS	107 (13.5)	175 (15.4)	266 (13.1)	256 (5.7)
Clopidogrel	47 (6.0)	72 (6.4)	136 (6.7)	276 (6.2)
PPI on arrival	196 (25.0)	297 (26.2)	611 (30.1)	264 (5.9)
Warfarin	58 (7.4)	93 (8.3)	192 (9.5)	278 (6.2)
Laboratory parameters				
Haemoglobin (mean,sd)	10.2 (3.2)	10.7 (3.3)	10.8 (3.1)	298 (6.7)
Urea (Median, IQR)	10.2 (6.2 to 16.8)	9.3 (5.4 to 15.0)	8.6 (5.2 to 14.7)	483 (10.8)
Prolonged coagulation	122 (14.6)	143 (12)	272 (12.6)	0 (0)
Co-morbidities				
Ischaemic heart disease	170 (20.4)	230 (19.3)	472 (21.9)	0 (0)
Dementia	38 (4.6)	45 (3.8)	109 (5.1)	0 (0)
Cirrhosis	46 (5.6)	44 (3.7)	73 (3.4)	45 (1.0)
Renal disease	69 (8.4)	96 (8.1)	184 (8.6)	53 (1.2)
Stroke	61 (7.3)	76 (6.4)	175 (8.1)	0 (0)
Cancer	67 (8.0)	78 (6.6)	192 (8.9)	0 (0)
Respiratory disease	88 (10.6)	114 (9.6)	265 (12.3)	0 (0)
Cardiac failure	40 (4.8)	67 (5.6)	138 (6.4)	0 (0)
Endoscopic Findings				
Stigmata of bleeding				
No Stigmata	437 (52.4)	853 (71.7)	1783 (82.6)	0 (0)
Low risk stigmata	15 (1.8)	26 (2.2)	35 (1.6)	0 (0)
High risk stigmata	382 (45.8)	311 (26.1)	340 (15.8)	0 (0)
Therapeutic endoscopy	283 (34.1)	234 (19.8)	256 (11.9)	59 (1.3)
Time to endoscopy (median, IQR)- hours	6.2 (3.6 to 9.1)	18.3 (15.4 to 21.4)	52.7 (36.0 to 93.1)	296 (6.6)

*Summary measures are reported for 4182 of the 4478 patients, as 296 (6.6%) have missing data for time to endoscopy

** Number (%) with missing data refers to all 4478 patients

4.4.2 Impact of time-to-endoscopy on mortality

6.5% of patients died (291/4478). Unadjusted analyses demonstrate that patients endoscoped within 12 hours had a higher mortality than those endoscoped between 12-24 hours, or >24 hours (crude mortality 9.0% versus 6.3% versus 5.4% respectively; OR for death 0.84, 95% CI 0.76-0.92 for 12-24 hours, and OR 0.76, 95% CI 0.65-0.88 for >24 hours; p<0.001) ***(Tables 4.2 and 4.3).*** However after adjustment for confounding variables there was no difference in mortality between those patients who were endoscoped early (<12 hours) or later (12-24 hours, OR 0.99, 95% CI 0.97-1.02; or >24 hours OR 0.98, 95% CI 0.88-1.09) ***(Table 4.3).*** There was no difference in mortality when comparing patients endoscoped between 12-24 hours and >24 hours (OR 1.17, 95% CI 0.87-1.58, p=0.29); similar results were seen with the sensitivity analysis testing for the possibility of a "tie-breaker bias" around 24 hours (comparing endoscopy at 12-22 hours vs. >26 hours; OR=1.07, 95% CI 0.82 to 1.35, p=0.35).

4.4.3 Impact of time-to-endoscopy on further bleeding

Further bleeding after the index endoscopy occurred in 11.9% of patients (533/4478) ***(Table 4.2).*** Patients endoscoped within 12 hours were more likely to experience further bleeding compared to those endoscoped between 12-24 hours or >24 hours (19.7% versus 10.9% versus 8.8% respectively; unadjusted OR's for further bleeding 0.75, 95% CI 0.69-0.81 at 12-24 hours; 0.63, 95% CI 0.56-0.72 at >24 hours; p<0.001) ***(Table 4.3).*** After adjustment for confounding variables there was no difference in the odds ratio for further bleeding between early (<12 hours) and later endoscopy (12-24 hours OR 0.99, 95% CI 0.96-1.01; or > 24 hours OR 0.95, 95% CI 0.87-1.04) ***(Table 4.3).***

Table 4.2: Outcome summaries

Outcome	Time to endoscopy <12 hours (n=834)	Time to endoscopy 12-24 hours (n=1190)	Time to endoscopy >24 hours (n=2158)	Time to endoscopy missing (n=296)
Death	75 (9.0)	75 (6.3)	117 (5.4)	24 (8.1)
Surgery/Radiology	63 (7.6)	39 (3.3)	47 (2.2)	13 (4.4)
Further bleeding	164 (19.7)	130 (10.9)	190 (8.8)	49 (16.6)
RBC transfusion	410 (49.2)	442 (37.1)	685 (31.7)	117 (39.5)
LOS (median, IQR)	6 (2-15)	5 (2-11)	7 (4-17)	29 (5-29)

Table 4.3: Odds Ratios for outcome of NVUGIB according to time to endoscopy- Unadjusted and Adjusted for disease severity‡

Outcome	Time to Endoscopy*	Unadjusted OR, 95% CI			Adjusted OR, 95% CI		
		OR**	95% CI	p	OR**	95% CI	p
Death	<12 hours	-	-	<0.001	-	-	0.70
	12-24 hours	0.84	0.76-0.92		0.99	0.97-1.02	
	>24 hours	0.76	0.65-0.88		0.98	0.88-1.09	
Further bleeding	<12 hours	-	-	<0.001	-	-	0.27
	12-24 hours	0.75	0.69-0.81		0.99	0.96-1.01	
	>24 hours	0.63	0.56-0.72		0.95	0.87-1.04	
Surgery/ radiology	<12 hours	-	-	<0.001	-	-	0.50
	12-24 hours	0.61	0.52-0.70		0.99	0.94-1.03	
	>24 hours	0.37	0.28-0.50		0.95	0.80-1.11	
RBC transfusion	<12 hours	-	-	<0.001	-	-	<0.001
	12-24 hours	0.73	0.69-0.78		0.81	0.74-0.89	
	> 24 hours	0.54	0.48-0.61		0.66	0.55-0.80	
LOS † (presented as difference in mean days)	<12 hours	-	-	<0.001	-	-	<0.001
	12-24 hours	0.48	0.40-0.56		0.44	0.36-0.52	
	>24 hours	1.83	1.52-2.14		1.69	1.39-1.99	

*Median time to endoscopy in each group: <12 hours= 6.2 hrs; 12-24 hours= 18.3 hrs; >24 hours= 52.7 hrs; **Reference category <12 hours OR= 1.0

† Length of hospital stay is not represented by an odds ratio, but rather by a difference in the mean length of stay in days.

‡ Model adjusted for age, presentation with shock, co-morbid illnesses (ischaemic heart disease, heart failure, respiratory disease, cancer, stroke, dementia, cirrhosis and renal failure), presentation with frank haematemesis or melaena, Hb and urea concentration on admission, a prolonged coagulation screen on admission, use of NSAIDS, warfarin, or PPIs, severity of endoscopic stigmata and admission status (new admission versus in-patient).

4.4.4 Impact of time-to-endoscopy on surgical or radiological intervention

Overall 3.6% (162/4478) patients had either surgical and/or radiological intervention to control bleeding ***(Table 4.2).*** Patients endoscoped within 12 hours were more likely to undergo surgical and/or radiological intervention compared to those endoscoped between 12-24 hours or >24 hours (7.6% versus 3.3% versus 2.2% respectively; unadjusted OR's 0.61, 95% CI 0.52-0.70 at 12-24 hours; 0.37, 95% CI 0.28-0.50 at >24 hours; p<0.001) ***(Table 4.3).*** After adjusting for confounders there was no difference in the need for surgical and/or radiological intervention to control bleeding between early (<12 hours) versus later endoscopy (12-24 hours OR 0.99, 95% CI 0.94-1.03; or > 24 hours OR 0.95, 95% CI 0.80-1.11) ***(Table 4.3).***

4.4.5 Impact of time-to-endoscopy on RBC transfusion

Overall, 1654/4478 (37%) patients received red blood cell (RBC) transfusion ***(Table 4.2).*** Patients endoscoped within 12 hours were more likely receive RBC transfusion than those undergoing endoscopy at 12-24 hours or >24 hours (49.2% versus 37.1% versus 31.7% respectively; unadjusted OR's 0.73, 95% CI 0.69-0.78 at 12-24 hours; 0.54, 95% CI 0.48-0.61 at >24 hours; p<0.001). After adjusting for confounders this trend persisted, with only a minor reduction in the OR's for receipt of RBC transfusion (12-24 hours OR 0.81, 95% CI 0.74-0.89, or > 24 hours OR 0.66, 95% CI 0.55-0.80) ***(Table 4.3).***

4.4.6 Impact of time-to-endoscopy on length of hospital stay

The greater the delay to endoscopy, the longer the time to hospital discharge, and this was the case for both unadjusted and adjusted analyses ***(Table 4.3).*** For example, after

adjustment for confounders, patients endoscoped >24 hours remained in hospital a mean 1.7 days longer (95% CI 1.39-1.99) than those endoscoped <12 hours.

4.4.7 Subgroup analyses for mortality, further bleeding, RBC transfusion and length of stay in patients requiring therapeutic endoscopy

The outcomes between patients who received a therapeutic endoscopy following presentation with NVUGIB and those who did not are detailed in ***Tables 4.4-4.5***. 61% of patients with high risk endoscopic stigmata received therapeutic endoscopy, while 5% of patients with low risk endoscopic stigmata received therapeutic endoscopy. There was no difference in the association between time to endoscopy and mortality between patients who received a therapeutic endoscopy and those who did not (p=0.63). The same applied to those having surgical or radiological intervention and for RBC transfusion. Although the effect of time to endoscopy on further bleeding differed between those who did and did not receive a therapeutic endoscopy (p=0.003), the risk-adjusted trend for further bleeding in those having later endoscopy just fell short of significance (OR 1.03, 95% CI 0.99-1.08 at 12-24 hours; OR 1.13, 95% CI 0.97-1-32 at >24 hours).

Earlier endoscopy was associated with a shorter risk-adjusted LOS ***(Table 4.4).*** There was a trend towards a more pronounced impact on LOS for patients needing therapeutic endoscopy. The mean LOS was increased by 2.4 days for those endoscoped >24 hours versus <12 hours in the therapeutic endoscopy group, compared to an increase of 1.6 days in those who did not undergo therapeutic endoscopy (p=0.09).

Table 4.4: Outcome summaries according to receipt of therapeutic endoscopy

	No therapeutic endoscopy			Received therapeutic endoscopy		
	<12 hours (n=548)	12-24 hours (n=951)	>24 hours (n=1894)	<12 hours (n=283)	12-24 hours (n=234)	>24 hours (n=256)
Death	45 (8.2)	54 (5.7)	95 (5.0)	30 (10.6)	21 (9.0)	22 (8.6)
Surgery/Radiology	31 (5.7)	23 (2.4)	29 (1.5)	32 (11.3)	16 (6.8)	18 (7.0)
Further bleeding	87 (15.9)	72 (7.6)	129 (2.8)	76 (26.9)	57 (24.4)	61 (23.8)
RBC transfusion	213 (38.9)	302 (31.8)	538 (28.4)	194 (68.6)	138 (59.0)	146 (57.0)
LOS (median, IQR)	4 (1-12)	4 (2-10)	6 (3-16)	8 (4-21)	6 (4-14)	10 (6-23)

*Results only reported for 4166/4478 as 312 of patients have missing data for time to endoscopy or whether they received a therapeutic endoscopy.

Table 4.5: Adjusted Odds Ratios for outcome of NVUGIB according to use of therapeutic endoscopy‡

	Time to endoscopy	No therapeutic endoscopy (OR, 95% CI)	Had therapeutic endoscopy (OR, 95% CI) †	P-value for interaction**
Death	<12 hours	-	-	0.63
	12-24 hours	0.99 (0.96 to 1.02)	1.00 (0.94 to 1.07)	
	>24 hours	0.95 (0.85 to 1.07)	1.01 (0.80 to 1.28)	
Further bleeding	<12 hours	-	-	0.003
	12-24 hours	0.95 (0.92 to 0.99)	1.03 (0.99 to 1.08)	
	>24 hours	0.83 (0.73 to 0.95)	1.13 (0.97 to 1.32)	
Surgery/Radiology	<12 hours	-	-	0.49
	12-24 hours	0.97 (0.92 to 1.02)	0.93 (0.82 to 1.05)	
	>24 hours	0.90 (0.74 to 1.09)	0.75 (0.46 to 1.22)	
RBC transfusion	<12 hours	-	-	0.74
	12-24 hours	0.79 (0.71 to 0.89)	0.76 (0.63 to 0.93)	
	>24 hours	0.64 (0.51 to 0.79)	0.59 (0.40 to 0.87)	
LOS *	<12 hours	-	-	0.09
	12-24 hours	0.42 (0.34 to 0.50)	0.62 (0.40 to 0.85)	
	>24 hours	1.62 (1.31 to 1.93)	2.39 (1.53 to 3.25)	

* Length of hospital stay is not represented by an odds ratio, but rather by a difference in means

**Reference category <12 hours OR= 1.0

†An interaction test was used to determine whether there was a difference in odds ratios between patients who had a therapeutic endoscopy and those who did not.

‡ Model adjusted for age, presentation with shock, co-morbid illnesses (ischaemic heart disease, heart failure, respiratory disease, cancer, stroke, dementia, cirrhosis and renal failure), presentation with frank haematemesis or melaena, Hb and urea concentration on admission, a prolonged coagulation screen on admission, use of NSAIDS, warfarin, or PPIs, severity of endoscopic stigmata and admission status (new admission versus in-patient).

4.5 Discussion

In line with recommendations from an editorial in a leading Endoscopy journal (Spiegel, 2009), this study provides an assessment of the independent effect of early endoscopy on mortality through adjustment for important and detailed disease specific prognostic variables. Key findings of this study are that:

1. Patients undergoing earlier endoscopy were predictably more likely to be shocked, have high risk stigmata at endoscopy, die, experience further bleeding and require surgical intervention. However after risk-adjustment, time to endoscopy had no impact on mortality or need for surgical or radiological intervention.
2. Amongst all patients earlier endoscopy was associated with a significant reduction in risk-adjusted length of hospital stay.
3. In patients who received therapeutic endoscopy (i.e. high risk patients) there was evidence of a trend towards an increased risk of further bleeding associated with later endoscopy, although this fell short of statistical significance.
4. The earlier an endoscopy was performed, the more likely patients were to receive RBC transfusion.

The inability to detect a reduction in mortality through earlier endoscopy is consistent with the existing body of evidence, mainly from other observational studies or small randomised trials (Bjorkman et al., 2004; Cooper et al., 2009; Lee et al., 1999; Lin et al., 1996; Spiegel et al., 2001). As might be expected in patients with more serious bleeding there is an inevitable selection bias towards a worse outcome with early endoscopy, because those who are more critically unwell are selected for early endoscopy. Thus it is conceivable that both the inability of this and previous studies to

detect a mortality reduction through performance of earlier endoscopy may represent residual confounding, despite detailed adjustment for potential confounders using a range of known and potential prognostic factors. Whilst there is little doubt that early endoscopy is likely to be life-saving in a small sub-group of patients, only a very large randomised trial is likely to have sufficient power to detect this and such a study would be challenging both logistically and ethically to conduct.

No relationship was demonstrated between early endoscopy and the need for surgery. Indeed, only two previous studies have: the first was a retrospective analysis of 909 patients presenting with NVUGIB across 13 centers in the USA, limited to the subgroup of patients with high risk stigmata (Cooper et al., 1999). The second (and more recent) was a retrospective analysis of administrative data from 2,592 patients with bleeding peptic ulcer limited to patients over the age of 66 (Cooper et al., 2009).

Early endoscopy was associated with a shorter risk-adjusted LOS, in keeping with previous studies (Cooper et al., 2009; Cooper et al., 1999). Patients endoscoped within 12 hours had half a day less in hospital (mean 11 hours) compared to those endoscoped between 12-24 hours, while those endoscoped after 24 hours stayed in hospital a mean 41 hours longer than those endoscoped within 12 hours, indicating that access to endoscopy was the main factor controlling length of stay. The reductions in LOS were even more pronounced in the higher risk subgroup of patients requiring therapeutic endoscopy. Although economic costs associated with hospitalisation for GI bleeding are currently not available in the UK, a study from the USA has estimated cost savings of $1594 (approx £1060) per patient largely through a 1 day reduction in LOS through performance of early endoscopy (Lee et al., 1999). Since many UK hospitals admit one or more patients a day with NVUGIB, the potential savings through provision of earlier

endoscopy could be substantial, given the economic consequences of a longer LOS are likely to outweigh the cost of providing sufficient endoscopic capacity to meet the demand of early endoscopy for patients with AUGIB.

In those patients who had a therapeutic endoscopy there was a trend towards increased further bleeding associated with later endoscopy, in that there was a 13% increased risk of further bleeding in patients who were endoscoped after 24 hours, although this fell short of statistical significance. Only one previous study has demonstrated a reduction in the risk of further bleeding through early endoscopy in high risk patients requiring therapeutic endoscopy (Cooper et al., 1999). Conversely, in the group of patients not requiring therapeutic endoscopy there was some evidence of a lower risk of further bleeding associated with later endoscopy, such that there was a 17% reduced risk of further bleeding in patients who were endoscoped after 24 hours, presumably because these patients had the least severe NVUGIB with the decline in further bleeding rates over time reflecting the natural course of the condition.

With regard to RBC transfusion, only one small trial has demonstrated a reduction in transfusion requirements through early endoscopy and only in a subgroup presenting with a bloody naso-gastric aspirate (Lin et al., 1996). In this study the opposite was found: patients having earlier endoscopy were more likely to receive RBC transfusion, whether for higher risk patients who received therapeutic endoscopy, or lower risk patients. There are three possible reasons. Firstly, patients due for earlier endoscopy may be more aggressively and perhaps, given associations between early RBC transfusion and further bleeding (Hearnshaw et al., 2010), inappropriately resuscitated with RBCs before the procedure, although this remains an area for future research (Jairath et al., 2010). Secondly RBC transfusion is subject to such widespread variation

in practice in NVUGIB that it is a subjective end-point. Another possibility is of unrecognised confounding although this seems unlikely given the clear differences in outcomes for mortality or need for surgery after adjusting for confounders. It was possible in our study to adjust for a range of known disease-specific prognosticators, which other studies, mainly those conducted using administrative databases, have been unable to achieve.

Despite UK, Scottish and international guidelines recommending that endoscopy should be performed where possible within 24 hours of presentation (Palmer, 2002; Management of acute upper and lower gastrointestinal bleeding - Scottish Intercollegiate Guidlelines Network 2008), it was notable that only 48% of endoscopies were performed within 24 hours and that only 61% of patients classified with high risk stigmata of bleeding received therapeutic intervention (Hearnshaw et al., 2010). In view of the unequivocal evidence of the benefits from endoscopic therapy, the shortcomings in the use of endoscopic therapy identified in this study is an important and previously unreported deficiency in UK endoscopy service provision. Specific details on the use of endoscopic therapy in this study have been previously described (Hearnshaw et al., 2010). Whilst the ideal may be that no patient with NVUGIB should wait longer than 24 hours for an endoscopy, this may not be achievable in all acute UK hospitals. At the time this audit was performed only 52% of hospitals in the UK had access to a formal out of hours endoscopy service (Hearnshaw et al., 2010). It is clear from this study that performance of endoscopy within 24 hours for all patients with NVUGIB is associated with a materially shorter LOS. This must be balanced against the costs of providing 24/7 access to endoscopy by skilled endoscopists and nursing staff. To endoscope most patients within 24 hours, there must also be provision for endoscopy lists at weekends.

4.6 Summary

Whilst the inability of this study to detect a reduction in mortality by performance of earlier endoscopy could represent residual confounding, the results clearly demonstrate a substantial reduction in risk-adjusted LOS and potentially improved control of haemorrhage in higher risk patients, supporting the routine use of early endoscopy for NVUGIB unless specific contraindications exist. These results may help inform the debate about emergency endoscopy service provision for upper gastrointestinal bleeding.

5 Chapter Five

Use of surgery and radiological embolisation after failure to control bleeding following non-variceal upper gastrointestinal bleeding

5.1 Introduction

Since mortality rates are 4-5 fold greater in patients who experience further bleeding compared to those who do not, improving outcomes from NVUGIB requires a particular focus on the management of patients who experience further bleeding. Aside from resuscitation and repeat endoscopy, the role of surgery as a salvage procedure is well established.

In more recent years, there has been increasing availability of TAE as a minimally invasive alternative to surgery, with the obvious advantage of avoiding general anaesthesia and laparotomy in critically unwell and often elderly patients. However, there are no reports describing the modern day use or outcomes of patients following surgery and/or TAE in the UK or elsewhere, other than single centre studies or case series (Eriksson et al., 2008; Poultsides et al., 2008; Ripoll et al., 2004; Wong et al., 2011). The 2007 UK audit dataset provides a unique opportunity to characterise modern day practice and outcomes in those patients who require salvage treatments to control NVUGIB. These data may help to better define the role of TAE in the current management algorithm and to inform future research questions.

5.2 Aims

This analysis was performed with the following aims:

1. To characterise the clinical features and outcomes of patients undergoing salvage surgery, TAE or repeat endoscopy following failed endoscopic haemostasis for NVUGIB.
2. To identify simple clinical parameters predicting failure of endoscopic therapy, in order to facilitate early identification and risk stratification of patients likely to require a salvage procedure.

5.3 Methods

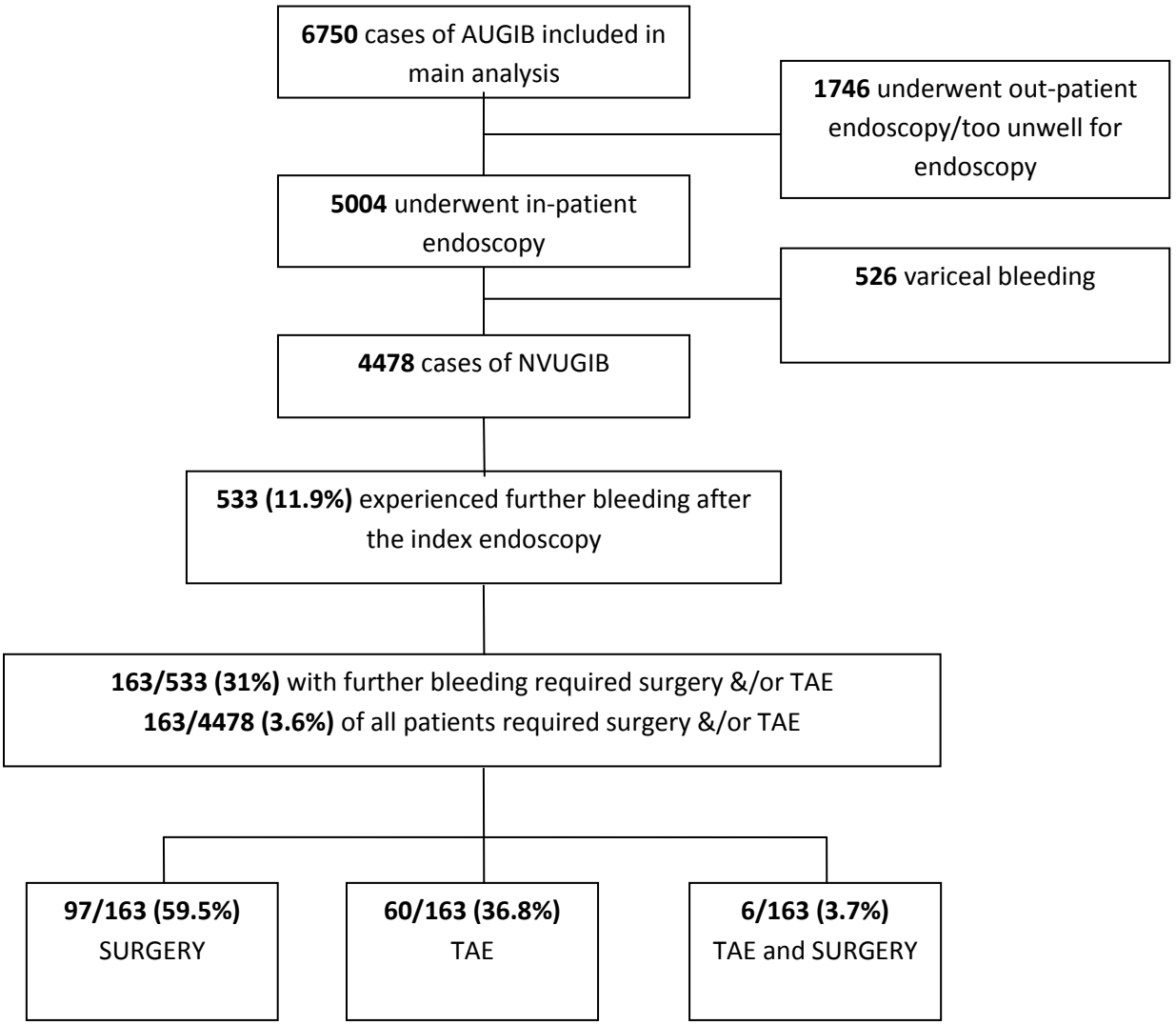
5.3.1 Statistical methods

A logistic regression model was used to identify clinical predictors of endoscopic failure. The model was adjusted for a pre-specified set of potentially confounding variables and potential predictors of mortality, selected from a list of variables based on clinical relevance among baseline clinical characteristics, endoscopic findings, pharmacological therapies and admission status. These variables were: age, presentation with shock, ≥2 co-morbid illnesses (ischaemic heart disease, heart failure, respiratory disease, cancer, stroke, dementia, cirrhosis and renal failure), presentation with frank haematemesis, presentation with melaena, Hb at presentation, urea concentration on admission, a prolonged coagulation screen, use of NSAIDS, clopidogrel, aspirin, warfarin, or PPIs, severity of endoscopic stigmata (blood in the upper GI tract, visible vessel, spurting vessel, adherent clot, dark spot) and admission status (new admission versus in-patient).

5.4 Results

89% (4478/5004) of all patients who underwent an in-patient endoscopy had an endoscopically confirmed non-variceal source of bleeding. In total, 11.9% (533/4478) of patients experienced further bleeding of whom 31% (163/533) went on to require salvage surgery (97/163), TAE (60/163) or both (6/163) to control bleeding ***(Figure 5.1)***.

Figure 5.1: Case ascertainment and use of surgery/radiological embolisation



5.4.1 Patient characteristics

The baseline clinical characteristics of patients undergoing surgery, TAE, surgery and TAE, and endoscopy alone are summarised in ***Table 5.1.*** There were some differences in the baseline characteristics of patients undergoing surgery compared to TAE; patients in the surgery group were older (71 years vs. 66.5 years), more likely to present with shock (65% vs. 62%), haematemesis (42.% vs. 22%), to have a clinical Rockall score of ≥3 (65% vs. 57%), a lower Hb (8.1 g/dL vs. 8.8 g/dL), coagulopathy (35.1% vs. 18.3%) and ≥2 co-morbidities (17% vs. 13%).

Table 5.1: Baseline characteristics of patients

	Surgery (n=97)	TAE (n=60)	Surgery and TAE (n=6)	Endoscopy only (n=4315)	Proportion of data missing (n, %) (n=4478)
Baseline characteristics					
Age (mean, SD)	71.2 (14.0)	66.5 (17.0)	70.2 (11.2)	66.6 (18.6)	0 (0)
Male (n, %)	52 (53.6)	37 (61.7)	5 (83.3)	2591 (60.1)	2 (0)
New admission (n, %)	76 (79.2)	42 (71.2)	3 (50.0)	3536 (83.0)	57 (1.3)
Disease presentation					
Shock (n, %)	63 (65.0)	37 (61.7)	4 (66.7)	1500 (35.4)	80 (1.8)
Haematemesis (n, %)	41 (42.3)	13 (22.0)	4 (66.7)	1426 (33.1)	3 (0.1)
Melaena (n, %)	66 (68.0)	42 (71.2)	4 (66.7)	2405 (55.8)	3 (0.1)
Clinical Rockall score (Mean, SD)	3.3 (1.7)	3.1 (1.8)	4.7 (1.5)	2.5 (1.8)	0 (0)
Clinical Rockall score >= 3 (high risk) (n, %)	63 (65.0)	34 (56.7)	5 (83.3)	2170 (50.3)	0 (0)
Total Rockall Score (Mean, SD)	6.0 (2.1)	4.7 (2.5)	7.2 (1.9)	3.8 (2.3)	15 (0.3)
Drug history (n,%)					
Aspirin	35 (39.3)	19 (33.9)	3 (60.0)	1379 (33.6)	228 (5.1)
NSAIDS	14 (15.9)	12 (21.4)	1 (20.0)	554 (13.6)	256 (5.7)
Clopidogrel	6 (6.7)	3 (5.6)	0 (0)	264 (6.5)	276 (6.2)
PPI	21 (23.9)	20 (35.7)	2 (40.0)	1143 (28.1)	264 (5.9)
Warfarin	6 (6.8)	7 (12.7)	0 (0)	355 (8.8)	278 (6.2)
Laboratory parameters					
Haemoglobin (mean, SD)	8.1 (2.7)	8.8 (3.1)	6.3 (2.1)	10.7 (3.2)	298 (6.7)
Urea (median, IQR)	12.6 (7.1 to 18.2)	10.1 (7 to 18.1)	7.1 (7 to 14)	9 (5.4 to 14.9)	483 (10.8)
Coagulopathy* (n, %)	34 (35.1)	11 (18.3)	2 (33.3)	535 (12.4)	0 (0)
Creatinine (median, IQR)	90 (67 to 121)	91 (72 to 130)	74 (55 to 95)	90 (74 to 116)	395 (8.8)
Co-Morbidities (n,%)					
Ischaemic heart disease	21 (21.7)	10 (16.7)	0 (0)	902 (20.9)	0 (0)
Dementia	3 (3.1)	1 (1.7)	0 (0)	202 (4.7)	0 (0)
Cirrhosis	5 (5.2)	4 (6.8)	2 (33.3)	168 (3.9)	45 (1.0)
Renal disease	6 (6.2)	4 (6.8)	1 (16.7)	370 (8.7)	53 (1.2)
Stroke	5 (5.2)	3 (5.0)	0 (0)	324 (7.5)	0 (0)
Cancer	7 (7.2)	7 (11.7)	1 (16.7)	357 (8.3)	0 (0)
Respiratory disease	13 (13.4)	9 (15.0)	1 (16.7)	484 (11.2)	0 (0)
Cardiac failure	7 (7.2)	4 (6.7)	1 (16.7)	257 (6.0)	0 (0)
≥ 2 co-morbidities	16 (16.5)	8 (13.3)	1 (16.7)	735 (17.0)	0 (0)

*Defined as an INR>1.5 or prothrombin time > 3 secs prolonged.

5.4.2 Endoscopic procedures and transfusion of blood components

Compared to the group undergoing TAE only, a greater proportion of patients in the surgery group underwent only one endoscopy prior to salvage procedure (69% vs. 53%), were reported to have high risk stigmata of haemorrhage (86% vs. 43%) at the index endoscopy and received a therapeutic procedure at the index endoscopy (56% vs. 25%) ***(Table 5.2)***. A similar proportion of patients in the surgery and TAE groups underwent endoscopy within 24 hours of presentation (70% vs. 66% respectively). A greater proportion of patients in the surgery group received RBC transfusions (94% vs. 78%), FFP (46% vs. 20%) and platelets (23% vs. 12%) compared to the TAE group during admission, although the median numbers of units of each blood component transfused per patients was similar in both groups.

Table 5.2: Endoscopic, transfusion and clinical outcome data

	Surgery (n=97)	TAE (n=60)	Surgery and TAE (n=6)	Endoscopy only (n=4315)	Proportion of data missing (n, %) (n=4478)
Endoscopic data					
No. of endoscopies (n, %)					0 (0)
1	67 (69.1)	32 (53.3)	4 (66.7)	3946 (91.5)	-
2	24 (24.7)	17 (28.3)	1 (16.7)	328 (7.6)	-
3	4 (4.1)	8 (13.3)	1 (16.7)	32 (0.7)	-
4+	2 (2.1)	3 (5.0)	0 (0)	9 (0.2)	-
Had a therapeutic endoscopy (n, %)	53 (55.8)	15 (25.0)	1 (16.7)	764 (17.9)	59 (1.3)
No. of therapeutic procedures (n, %)					72 (1.6)
1	36 (38.3)	5 (8.3)	0 (0)	461 (10.9)	-
2	11 (11.7)	8 (13.3)	1 (16.7)	266 (6.3)	-
3+	4 (4.3)	2 (3.3)	0 (0)	19 (0.5)	-
High risk stigmata (n, %)	83 (85.6)	26 (43.3)	5 (83.3)	999 (23.2)	0 (0)
Time to Index endoscopy (n, %)					296 (6.6)
<12 hours	40 (45.5)	21 (36.2)	2 (50.0)	771 (19.1)	-
12-24 hours	21 (23.9)	17 (29.3)	2 (50.0)	1150 (28.5)	-
>24 hours	27 (30.7)	20 (34.5)	0 (0)	2111 (52.4)	-
Blood components transfused					
Received RBCs within 12 hours (n, %)	83 (85.6)	41 (68.3)	6 (100)	1524 (35.3)	0 (0)
Received RBCs (n, %)	91 (93.8)	47 (78.3)	6 (100)	2043 (47.4)	0 (0)
Number of RBC units received (median, IQR)	9 (5 to 14)	8 (3 to 12)	22 (13 to 25)	3 (2 to 4)	236 (10.8)
Received FFP (n, %)	45 (46.4)	12 (20.0)	4 (66.7)	206 (4.8)	0 (0)
Number of FFP units received (median, IQR)	4 (4 to 8)	4.5 (3.5 to 10)	4 (3 to 8.5)	3 (2 to 4)	0 (0)
Received platelets (n, %)	22 (22.7)	7 (11.7)	2 (33.3)	68 (1.6)	0 (0)
Number of platelet units received (median, IQR)	2 (1 to 3)	2 (1 to 2)	1.5 (1 to 2)	2 (1 to 3)	0 (0)
Outcome summaries					
In-hospital mortality n(%)	28 (28.9)	6 (10.0)	3 (50.0)	254 (5.9)	0 (0)
LOS (median, IQR)*	19 (12 to 19)	17.5 (7 to 29)	29 (7 to 29)	6 (3 to 15)	298 (6.7)
Units of RBCs transfused (median, IQR)	9 (5 to 14)	8 (3 to 12)	22 (13 to 25)	3 (2 to 4)	236 (10.8)

*Data values were censored at 29 days

5.4.3 Details of surgical and transcatheter arterial embolisation procedures

Surgery was undertaken in 2.3% (103/4478) of patients ***(Table 5.3).*** The median time from presentation to index endoscopy in the group receiving surgery was 13.7 hours (iqr 5.1 to 24.9 hours). The median number of days from index endoscopy to surgery was 1 day (iqr 0 to 4 days) and from presentation to surgery was 2 days (iqr 1 to 6 days). 38% (34/90) of operations took place between 0800-1700, Monday to Friday, with 21% (19/90, data missing for 13 patients) of all surgery taking place between the hours of midnight to 0800, Monday to Sunday. The most common indication for surgery was uncontrolled bleeding (83%, 85/103) and the most commonly performed surgical procedure was an oversew (41%, 40/103) or under-run (28%, 27/103) of an ulcer. A consultant surgeon was present at 89% (86/97) of all operations, (data missing for 6 patients) and was listed as the lead surgeon in 78% (76/97) of operations (data missing for 6 patients). A consultant anaesthetist was present at 76% (63/83) of all operations (data missing for 20 patients).

1.4% (60/4478) of patients presenting with NVUGIB underwent TAE only and a further 6 patients underwent TAE followed by surgery ***(Table 5.4)***; in these 6 patients there was further bleeding despite TAE, necessitating surgery.

Table 5.3: Details of surgical procedure undertaken

	Patients who underwent Surgery (n, %) (n=103)*	Proportion of data missing (n, %)
Timing of surgery		
Weekend or weekday		5 (4.9)
Mon-Fri	74 (75.5)	-
Sat-Sun	24 (24.5)	-
Timing		13 (12.6)
Mon-Fri 0800-1700	34 (37.8)	-
Mon-Fri 1701-2359/Sat-Sun 0801-2359	37 (41.1)	-
Mon-Sun 0000-0759	19 (21.1)	-
Hours from presentation to index endoscopy (median, IQR)	13.7 (5.1 to 24.9)	11 (10.7)
Days from Index endoscopy to Surgery (median, IQR)	1 (0 to 4)	5 (4.9)
Days from presentation to Surgery (median, IQR)	2 (1 to 6)	8 (7.8)
Indication for surgery		
Uncontrolled bleeding	85 (82.5)	0 (0)
Peritonitis/perforation	7 (6.8)	0 (0)
Malignancy	5 (4.9)	0 (0)
Other	9 (8.7)	0 (0)
Surgical procedure		
Under-run of ulcer	27 (27.8)	6 (5.8)
Oversew of ulcer	40 (41.2)	6 (5.8)
Excision of ulcer	3 (3.1)	6 (5.8)
Excision of ulcer with vagotomy/pylorplasty	2 (2.1)	6 (5.8)
Partial Gastrectomy	9 (9.3)	6 (5.8)
Other	16 (16.5)	6 (5.8)
Grade of Lead Surgeon		
Consultant	76 (78.4)	6 (5.8)
Registrar (supervised)	10 (10.3)	6 (5.8)
Registrar (unsupervised)	7 (7.2)	6 (5.8)
Associate specialist/Staff grade	4 (4.1)	6 (5.8)
Grade of most senior anaesthetist		
Consultant	63 (75.9)	20 (19.4)
SpR	14 (16.9)	20 (19.4)
SHO	6 (7.2)	20 (19.4)
Other	0 (0)	20 (19.4)
Post-operative complications		
Pneumonia	22 (21.4)	0 (0)
Renal failure	11 (10.7)	0 (0)
Sepsis	9 (8.7)	0 (0)
Significant cardiac event	10 (9.7)	0 (0)
PE/DVT	2 (1.9)	0 (0)
Stroke	1 (1.0)	0 (0)
Wound dehiscence/infection	4 (3.9)	0 (0)
Liver failure	3 (2.9)	0 (0)

Table 5.4: Details of transcatheter arterial embolisation procedure

	Patients who underwent TAE (n, %) (n=66)	Proportion of data missing (n, %)
Underwent diagnostic angiography		
Underwent diagnostic angiography first	34 (75.6)	21 (31.8)
Bleeding source identified	21 (65.6)	34 (51.5)
Therapeutic angiography and embolisation	20 (43.5)	20 (30.3)
Bleeding successfully controlled	13 (68.4)	47 (71.2)
Other radiological procedure		
Other radiological procedure	7 (15.9)	22 (33.3)
Bleeding successfully controlled	3 (60.0)	61 (92.4)

5.4.4 Mortality, length of hospital stay and transfusion requirements in the surgery and transcatheter arterial embolisation groups

In-hospital mortality was 29% (28/97) in the patients who underwent surgery, 10% in patients who underwent TAE and 50% (3/6) in the six patients who required both TAE and surgery ***(Table 5.2)***. By comparison, the mortality in the group of patients not requiring a salvage procedure (i.e. having endoscopy only) was 5.9% (254/4315). Length of hospital stay and the number of RBCs transfused was similar between the surgery and TAE groups.

5.4.5 Clinical and endoscopic predictors of failure to achieve endoscopic haemostasis

Clinical and endoscopic predictors of failure to achieve endoscopic haemostasis are outlined in ***Table 5.5***. Clinical and laboratory parameters at presentation with NVUGIB (prior to endoscopy) most strongly associated with endoscopic failure were presentation with coagulopathy (OR 3.27, 95% CI 2.37 to 4.53, p<0.001), haemodynamic shock (OR 1.57, 95% CI 1.27 to 1.95, p<0.001), melaena (OR 1.54, 95% CI 1.21 to 1.96, p<0.001), urea ≥10 (OR 1.51, 95% CI 1.23 to 1.85, p<0.001) and a presenting Hb between 8.1 g/dL-10 g/dL (OR 2.22, 95% CI 1.71 to 2.87, p<0.001 for Hb 8.1-10 g/dL, OR 1.65, 95% CI 1.40 to 1.95, p<0.001 for < Hb 8.0 g/dL, compared to Hb > 10 g/dL). Endoscopic stigmata most strongly associated with failure to achieve haemostasis were fresh blood in the UGIT (OR 2.93, 95% CI 2.32 to 3.69, p<0.001), an adherent clot (OR 2.29, 95% CI 1.70 to 3.09, p<0.001) or a spurting vessel (OR 2.42, 95% CI 1.47 to 4.00, p<0.001).

Table 5.5: Clinical and endoscopic characteristics predictive of further bleeding*

	Further bleeding in patients without characteristic – n (%)	Further bleeding for patients with characteristic – n (%)	Odds Ratio	95% CI	p-value
Age >= 65	158 (9)	375 (14)	1.09	0.86 to 1.38	0.49
Male	185 (10)	347 (13)	1.36	1.09 to 1.70	0.006
In-hospital bleeding	383 (11)	144 (19)	1.54	1.20 to 1.98	0.001
NSAID use	434 (12)	70 (12)	0.94	0.69 to 1.28	0.68
PPI use	351 (12)	153 (13)	1.38	1.09 to 1.75	0.008
Aspirin use	325 (12)	186 (13)	0.81	0.64 to 1.03	0.08
Warfarin use	455 (12)	48 (13)	0.31	0.19 to 0.48	<0.001
Coagulopathy**	397 (10)	136 (23)	3.27	2.37 to 4.53	<0.001
Urea >= 10	153 (7)	306 (17)	1.51	1.23 to 1.85	<0.001
Hb					
Hb <8	-	208 (21)	1.65	1.40 to 1.95	<0.001
8 <= Hb<10	-	127 (15)	2.22	1.71 to 2.87	
Hb >10	-	155 (7)	1.00	-	-
>=2 co morbidities	408 (11)	125 (16)	1.06	0.81 to 1.39	0.66
Shock	228 (8)	300 (19)	1.57	1.27 to 1.95	<0.001
Haematemesis	366 (12)	165 (11)	1.05	0.82 to 1.33	0.72
Melaena	157 (8)	374 (15)	1.54	1.21 to 1.96	<0.001
Stigmata at index endoscopy					
Blood in UGIT	299 (8)	234 (30)	2.93	2.32 to 3.69	<0.001
Visible vessel	454 (11)	79 (27)	1.39	1.00 to 1.93	0.05
Spurting vessel	494 (11)	39 (41)	2.42	1.47 to 4.00	0.001
Adherent clot	430 (10)	103 (32)	2.29	1.70 to 3.09	<0.001
Dark spot in ulcer base	517 (12)	16 (19)	1.36	0.72 to 2.54	0.34

*overall, 533/4478 patients had further bleeding (11.9%)

**Defined as an INR>1.5 or prothrombin time > 3 secs prolonged.

5.5 Discussion

This study, the largest to date to report the use of surgery or TAE in patients presenting with NVUGIB, has shown that salvage procedures in the form of surgery or TAE are rarely used in the current management of NVUGIB. Less than 4% of all presentations with NVUGIB required either surgery or TAE to control bleeding, the remainder being managed endoscopically without those interventions. The rates of surgery in this study are similar to results from other recent large registries including the Canadian RUGBE data-base (Barkun et al., 2004), the Italian PNED database (Marmo et al., 2008) and from Hong Kong (Wong et al., 2011). Given that rates of surgery reported twenty years ago were as high as 15-20% (Dronfield et al., 1982; Jones et al., 1973; Masson et al., 1996), this is most likely to be a reflection of improvements in the use of endoscopic therapy and techniques, as well as, amongst other interventions, high dose proton pump inhibition.

Surgery has been the traditional salvage therapy in patients with uncontrolled bleeding or further bleeding which cannot be managed endoscopically. In this study 69% of patients had only one endoscopy prior to surgery suggesting that bleeding may have been torrential at the index endoscopy, or that an early decision was made not to repeat endoscopy in the event of further bleeding and go straight to surgery. The low rates of endoscopic therapy at the index endoscopy are surprising; one can speculate that this may have been due to torrential bleeding prohibiting the use of endoscopic therapy. The fact that 21% of all surgery took place between the hours of midnight-0800 reflects the emergency nature of patients presented to surgical colleagues. Despite the fact a consultant surgeon was present at 89% of all operations, the exceptionally high post-operative mortality of 29% is undoubtedly a reflection of patient age, co-morbidity and severity of bleeding.

In recent years, TAE has become available in some institutions as an alternative to surgery and has been proposed as a potentially less hazardous alternative to surgery, especially in the highest risk patients (Aina et al., 2001; Loffroy et al., 2008). The current study lends further support to its reported success given that only 9% had further bleeding after TAE necessitating surgery and 91% of patients requiring TAE as a salvage procedure survived. These rates of further bleeding after TAE compare favourably with those reported in the literature, ranging from 9-66% in radiological case series (Loffroy et al., 2010) and other single centre studies (Wong et al., 2011). In this study it was paradoxical that those patients who underwent surgery were older, had a greater degree of co-morbidities and appeared to present with more serious bleeding than those undergoing TAE, although the decision algorithm is most likely to reflect the limited availability of round the clock interventional radiology in most UK hospitals at the time of the audit.

TAE is sometimes used empirically in the absence of angiographic evidence of contrast extravasation, or even prophylactically in very high risk ulcers to prevent further bleeding, although we could not ascertain the frequency from the current study. Peptic ulcer bleeding can be intermittent, therefore contrast extravasation may not always be seen during diagnostic angiography; this may explain why a bleeding source was only reported to have been identified in 66% of cases in the present study. Although empirical embolisation remains an area of uncertainty, it is an important issue for future prospective studies, especially since rates of further bleeding have not substantially fallen in the interval between the two UK audits of 1993 (16% further bleeding rate) (Rockall et al., 1995) and 2007 (Hearnshaw, 2011).

The main barrier to using TAE as an alternative or adjunct to surgery for NVUGIB, is its availability. In 2009 <10% of all acute hospital trusts in the UK were able to provide 24 hour access to interventional radiology, although recent guidance from the Royal College of Radiologists has been issued in order to help increase the availability of this intervention around the clock (The Royal College of Radiologists. *Standards for Providing a 24-Hour Diagnostic Radiology Service*, London, 2009). This initiative, coupled with emerging technologies (Sung et al., 2011) and a greater proportion of variceal bleeding (Hearnshaw et al., 2010), is likely to lead to further reductions in surgery in coming years and an increasing use of TAE.

Close liaison between emergency medicine physicians, gastroenterologists, surgeons and interventional radiologists is important to facilitate early processes and algorithms of care in those patients who present with severe bleeding. We have identified clinical predictors that can be used at presentation to identify those patients more likely to fail endoscopic therapy. These include presentation with coagulopathy (INR >1.5), shock, urea>10 mmol/L and Hb <10 g/dL. These simple parameters could be used in addition to established risk scores to facilitate early recognition of patients who are more likely to fail endoscopic therapy.

It is not possible in this retrospective analysis to make a direct comparison of the outcomes of patients undergoing surgery or TAE. It is clear that the characteristics of patients in the two groups were different and that differing processes of care within institutions may have influenced the decision to send patients to surgery rather than embolisation. Other limitations of this study include lack of data relating to timing of TAE, technical details of the procedure (e.g. embolisation agent and technique) and missing data. Specific details of the embolisation procedure were not part of the

minimum data-set during the electronic submission of case report forms. Its strengths relate to its nationwide coverage and prospective data collection over a 2 month period, providing a “real-life” picture of processes of care and outcome data from most UK hospitals.

5.6 Summary

This study demonstrates that salvage surgery or TAE are required in <4% of patients in the modern day management of NVUGIB in the UK. The apparent success of TAE in this retrospective analysis, coupled with its increasing availability, warrants a prospective study to establish whether TAE could be used as a potentially less hazardous alternative to surgery in the management of patients who fail endoscopic therapy. A RCT in Hong Kong comparing surgery versus embolisation in high risk ulcers failing endoscopic haemostasis is currently listed as recruiting (Trans-Catheter Arterial Embolization and Surgery in Patients with Peptic Ulcer Bleeding Uncontrolled by Endoscopic Therapy. Study Identifier Nct00766961, accessed at www.Clinicaltrials.Gov) and this may provide important information to help define the place of TAE as an alternative to surgery in the current management algorithm of NVUGIB.

6 Chapter Six

Prevalence, management and outcomes of patients with coagulopathy following non-variceal upper gastrointestinal bleeding

6.1 Introduction

In other scenarios of major bleeding (e.g. trauma, cardiac surgery) the presence of a coagulopathy has been identified as a strong and independent risk factor for mortality. This has lead to changes in the approach to transfusion with earlier use of pro-haemostatic factors (e.g. FFP) to correct coagulopathy, with an apparent survival advantage in observational studies. The prevalence of coagulopathy, its management and association with clinical outcome is poorly characterised in patients with AUGIB. A better understanding may help to develop "haemostatic" transfusion strategies aimed to facilitate control of bleeding in patients with major haemorrhage.

6.2 Aims

The aim of this study was:

1. To characterise the epidemiology of a key marker of coagulopathy, prolongation of the INR, in patients presenting with AUGIB.
2. To describe the use of plasma transfusion to correct this.
3. To determine the association between coagulopathy, patient survival and other key clinical outcomes following AUGIB.

6.3 Methods

6.3.1 Defining coagulopathy

Standard laboratory tests to measure deranged coagulation are the prothrombin time (PT) and international normalised ratio (INR). PT results between hospitals could not be compared directly because differing thromboplastins are used in different laboratories, each with a different laboratory specific Mean Normal Prothrombin Time and International Specificity Index. Although the INR was originally developed to standardise assessment of the response to vitamin K antagonists, it does provide a standardised means of comparing coagulation derangements between laboratories. Therefore the presence of coagulopathy was based upon INR measurements. The threshold for defining coagulopathy was an INR≥1.5. This is a pragmatic definition used by most clinicians and is the threshold recommended by the BSG at which correction of coagulopathy should be considered in patients following AUGIB (Palmer, 2002).

6.3.2 Case selection

The analysis only evaluated patients whom underwent an in-patient endoscopy for bleeding (i.e. had clinically significant bleeding warranting an endoscopic examination). Patients with liver cirrhosis and variceal bleeding were excluded since they are likely to have pre-existing derangements in the PT or INR due to impaired synthesis of coagulation factors, have differing demographic features and outcomes (further bleeding and mortality rates) compared to those with NVUGIB and make up less than 10% of all presentations with AUGIB in the UK. Therefore this analysis was conducted only on those patients presenting with NVUGIB whom underwent endoscopic evaluation.

6.3.3 Statistical methods

To explore associations with outcomes, a logistic regression model was used to compare risk adjusted clinical outcomes in those with INR prolongation with those without INR prolongation. The three clinical outcomes of interest comparing the two groups were mortality, further bleeding and need for surgical/radiological intervention to control bleeding. A secondary analysis assessed whether the effect of INR prolongation on clinical outcomes was modified by the use of warfarin (i.e. whether the association between INR prolongation and outcome was different depending on whether the patient was taking warfarin). This was done by performing an interaction test.

The model was adjusted for a pre-specified set of potentially confounding variables, based on clinical characteristics, endoscopic findings, pharmacological therapies and admission status. These variables were: age, presentation with shock, ≥2 co-morbid illnesses (ischaemic heart disease, heart failure, respiratory disease, cancer, stroke, dementia, cirrhosis or renal failure), presentation with frank haematemesis, presentation with melaena, Hb at presentation, urea concentration on admission, use of NSAIDS, clopidogrel, aspirin, warfarin, or PPIs, severity of endoscopic stigmata and admission status.

In 47% of patients data were not available for at least one baseline clinical variable (mean number of missing baseline variables 0.9, iqr 0 to 1), which was account for by imputation. Because many of the patients without an INR available had a recorded PT result (n=1061, 60%), multiple imputation allowed use of the correlation between INR and PT results to obtain better estimates of missing INR values.

6.4 Results

There were 4478 patients with endoscopically confirmed NVUGIB. 84% (3782/4478) of all patients presenting with NVUGIB had a coagulation screen documented, of whom 72% (2709/3782) had an INR performed, 66% (2507/3782) a PT performed and 38% (1450/3782) had both an INR and PT performed. 95% of coagulation screens were undertaken on the day of presentation to hospital and although specific times were not recorded, these are likely to have been drawn upon first presentation to hospital. Of the 5% (n=112) of patients who did not have an INR screen on the same day as presentation, the majority had the screen the next day (n=83). More than 99% of patients had the screen within two days of presentation.

6.4.1 Prevalence and severity of INR prolongation

The prevalence of INR prolongation (≥1.5) following presenting with NVUGIB was 16.4% (444/2709) in those patients in whom an INR was recorded. In patients with a prolonged INR, 35% (154/444) had an INR between 1.5-2.0, 19% (86/444) an INR between 2.1-3.0 and 46% (204/444) an INR of >3.0.

6.4.2 Clinical characteristics of patients with INR prolongation

Patients with a prolonged INR were older, more likely to present with haemodynamic shock (45% vs. 36%), have a higher median clinical Rockall score (4 vs. 2), more likely to be high risk patients (defined as a clinical Rockall score ≥3) and have ≥two or more co-morbidities (29% vs. 15%), mainly ischaemic heart disease (34% vs. 19%) and congestive cardiac failure (15% vs. 5%) ***(Table 6.1)***. Those with a prolonged INR had a lower Hb (9.4g/dL vs. 10.7g/dL), a higher urea concentration (12.7 vs. 8.9) and were more likely to be taking warfarin (66% vs. 1%).

Table 6.1: Characteristics of patients with and without INR prolongation

	INR < 1.5 (n=2265)	INR >= 1.5 (n=444)	% with data unavailable*
Clinical features			
Age (mean, SD)	65.7 (18.6)	71.2 (14.9)	0
Male – no. (%)	1333 (59)	262 (59)	<1
New admission – no. (%)	1893 (85)	341 (77)	1
Disease presentation			
Shock – no. (%)	798 (36)	198 (45)	2
Haematemesis – no. (%)	736 (33)	130 (29)	<1
Melaena – no. (%)	1291 (57)	277 (62)	<1
Clinical Rockall score (median, IQR)	2 (1-4)	4 (2-5)	0
Medications			
Aspirin – no. (%)	755 (35)	85 (20)	5
NSAIDS – no. (%)	329 (15)	32 (7)	6
Warfarin – no. (%)	28 (1)	284 (66)	6
Laboratory parameters			
Haemoglobin (mean, SD)	10.7 (3.2)	9.4 (3.0)	7
Platelets (median, IQR)	41 (23-73)	29 (22-68)	98
Urea (median, IQR)	8.9 (5.5-14.7)	12.7 (7.1-20.5)	11
Creatinine (median, IQR)	89 (73-115)	106 (79-140)	9
Co-morbidities			
Ischaemic heart disease – no. (%)	437 (19)	151 (34)	0
Dementia – no. (%)	101 (4)	15 (3)	0
Renal disease – no. (%)	186 (8)	56 (13)	1
Stroke – no. (%)	146 (6)	42 (9)	0
Cancer – no. (%)	191 (8)	49 (11)	0
Respiratory disease – no. (%)	262 (12)	56 (13)	0
Cardiac failure – no. (%)	110 (5)	68 (15)	0
Two or more co-morbidities – no.(%)	343 (15)	128 (29)	0

6.4.3 Use of FFP in patients with and without INR prolongation

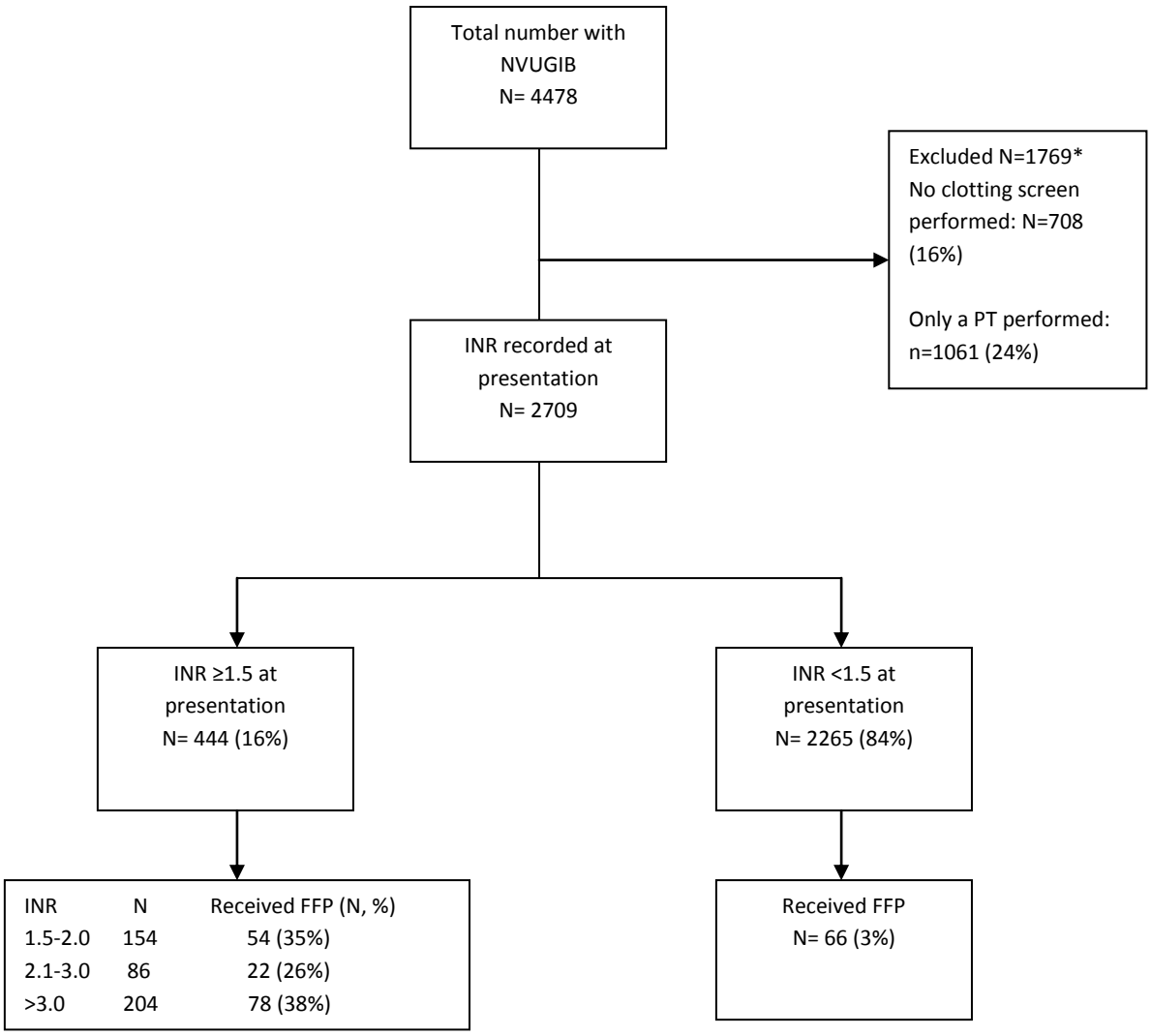
In terms of the use of blood components, patients with INR prolongation were more likely to be transfused with RBCs, including RBCs within 12 hours of presentation (70% vs. 48%), FFP (35% vs. 3%) and platelets (6% vs. 3%) ***(Table 6.2)***. At endoscopy, those with an INR prolongation were also more likely to have high risk endoscopic stigmata of haemorrhage (34% vs. 25%) ***(Table 6.2)***.

8% (220/2709) of patients who had an INR recorded received FFP transfusion during their admission ***(Figure 6.1)***. In those patients with an INR <1.5, 3% (66/2265) received FFP transfusion. In those patients with INR prolongation (≥1.5), only 35% (154/444) received FFP. Examining receipt of FFP stratified by presenting INR, 35% of those with an INR between 1.5-2.0 received FFP, 26% of those with an INR between 2.1-3.0 received FFP and 38% of those with an INR >3.0 received FFP.

Table 6.2: Use of Blood components and Endoscopy therapy in patients with and without INR prolongation

	INR < 1.5 (n=2265)	INR >= 1.5 (n=444)	%with data unavailable
Blood components			
RBCs within 12 hours	813 (36)	245 (55)	0
Received RBCs no. (%)	1091 (48)	310 (70)	0
Units of RBCs received (median, IQR)	4 (2-5)	4 (3-6)	11
Received FFP no. (%)	66 (3)	154 (35)	0
Units of FFP received (median, IQR)	4 (2-4)	4 (2-5)	0
Received platelets no. (%)	41 (2)	28 (6)	0
Units of platelets received (median, IQR)	2 (1-2)	2 (1-4)	0
Endoscopic data			
Had a therapeutic endoscopy – no. (%)	435 (19)	93 (21)	1
High risk Endoscopic stigmata – no. (%)	572 (25)	152 (34)	0
Time to Index endoscopy > 24 hours – no. (%)	1077 (50)	207 (51)	7

Figure 6.1: Prevalence of coagulopathy and receipt of fresh frozen plasma in patients with and without INR prolongation



*1769 patients with a missing coagulation screen were excluded from the descriptive statistics in tables 2-4. All patients were included in the logistic regression model by use of multiple imputation for missing data.

6.4.4 Outcomes of patients with INR prolongation

In-hospital mortality (15% vs. 6%), further bleeding (19% vs. 12%) and the need for salvage surgery/embolization (5% vs. 3%) was higher for patients with INR prolongation than those without, as was the median length of hospital stay ***(Table 6.3)***. After adjustment for confounding variables in a logistic regression model (age, presentation with shock, ≥2 co-morbid illnesses, presentation with frank haematemesis, presentation with melaena, Hb at presentation, urea concentration on admission, use of NSAIDS, clopidogrel, aspirin, warfarin, or PPIs, severity of endoscopic stigmata and admission status), the odds ratio for mortality in patients with INR prolongation compared to patients without INR prolongation was 5.63 (95% CI 3.09-10.27, $p<0.001$).

There was no evidence that INR prolongation was associated with further bleeding or need for surgery/radiological intervention ***(Table 6.4)***. There was no evidence that the use of warfarin modified the association between INR prolongation and clinical outcomes ((mortality OR 5.96 (no warfarin) vs. 3.29 (warfarin), $p=0.41$; further bleeding OR 1.10 (no warfarin) vs. 1.02 (warfarin), $p=0.54$; surgery OR 1.03 (no warfarin) vs. 1.02 (warfarin), $p=0.97$)).

Table 6.3: Outcome summaries in patients with and without INR prolongation

Clinical Outcomes	INR < 1.5 (n=2265) No. (%)	INR >= 1.5 (n=444) No. (%)	%with data unavailable*
Mortality	125 (6)	65 (15)	0
Further bleeding	265 (12)	83 (19)	0
Surgery/radiology	76 (3)	23 (5)	0
Length of Stay (days- median,IQR)	6 (3-14)	9 (5-22)	7

Table 6.4: Adjusted Odds ratios for clinical outcomes in patients with INR prolongation compared to those without INR prolongation

Clinical Outcomes †	Odds ratio*	95% CI	p-value
Mortality	5.63	3.09 to 10.27	<0.001
Further bleeding	1.05	0.93 to 1.18	0.44
Surgery/radiology	1.03	0.83 to 1.28	0.80

†Odds ratios for clinical outcomes are compared in those patients with an INR>1.5 versus those with an INR <1.5

*Reference category: INR <1.5, OR=1.0

6.5 Discussion

In this study 16% of presentations to hospital with NVUGIB and a recorded INR had evidence of a coagulopathy, defined pragmatically as an INR≥1.5. Patients with coagulopathy had greater severity of bleeding compared to those without coagulopathy, since they were more likely to present with haemodynamic shock, a lower Hb, higher urea concentration, require RBC transfusion within 12 hours of presentation and have greater severity of endoscopic stigmata of bleeding. After adjusting for a range of confounding variables to account for disease severity, patients with coagulopathy had more than a five-fold increased risk of in-hospital mortality compared to patients without coagulopathy.

No association was found between coagulopathy at presentation and the clinical endpoints of further bleeding or need for surgical/radiological intervention. Further bleeding, which must be distinguished from severity of bleeding at presentation, is a unique complication of upper gastrointestinal bleeding occurring in approximately 15% of cases after initial endoscopic haemostasis has been achieved, often within 3-5 days of presentation with the index bleed. Whilst it is clear that those patients with INR prolongation in this study had more severe bleeding at presentation, INR prolongation was not associated with the subsequent risk of further bleeding. Further bleeding *per se* is considered to be influenced by multiple interacting factors such as the severity of the endoscopic lesion, adequate use of endoscopic therapy, use of proton pump therapy and use other pharmacological agents, which in turn may have had a greater influence than the presenting INR on the subsequent risk of further bleeding (Elmunzer et al., 2008). The numbers of patients proceeding to surgery or radiological intervention were few and it is possible that co-morbidity in those with coagulopathy influenced decisions.

There was evidence of wide variation in the use of FFP. Broadly a third of all patients received plasma for INR groups 1.5-2, 2-3 and >3. Only 35% of patients presenting with an INR ≥1.5 in total were transfused FFP; in contrast 3% of presentations with an INR ≤1.5 also received FFP. These observations suggest clinical uncertainty as to optimal transfusion management and appears similar to the variation in practice seen in the management of coagulopathy in other critically ill patient cohorts (Walsh et al., 2010).

The strengths of this study include a large overall sample size, detailed description of clinical characteristics and nationwide geographical location of participating units suggesting the population studied was generalisable and the results typical of wider practice. Limitations in this study include the secondary analysis of prospectively collected data and the potential for residual confounding in the analysis. The range of known and suspected confounders adjusted for was, however, large, and it appears unlikely that unknown confounders would significantly reduce the strength of the observed association between coagulopathy and mortality. No data were collected on FFP dose and data were not available on the use of vitamin K as a corrective agent for INR prolongation. The cause of death as secondary to haemorrhage or other factors could not be differentiated. We identified patients taking warfarin, in whom elevations in INR would be expected, but there was no evidence that the use of warfarin affected the association between coagulopathy and mortality providing reassurance that the association between coagulopathy and mortality was not merely a reflection of a greater degree of co-morbidity in patients taking warfarin which could not be adjusted for in the analysis.

The mechanisms underlying coagulopathy in patients with AUGIB are unclear. Factors such as hypoxia, acidosis, hypothermia, anaemia and consumption may be relevant, or through a different cellular mechanism activating the coagulation cascade on the causal pathway to death. Alternatively, it may be an innocent bystander of poor prognosis. In either case, the results suggest that basic indices of coagulation which define coagulopathy identify a group of patients with a five-fold increase in the odds of in-hospital mortality. Whilst this study characterises contemporary practice in a large cohort of patients, it does not inform any benefit to patients of improving coagulopathy or transfusing FFP. Outcomes in new studies should include rates of further bleeding, given this endpoint has not improved much in longitudinal UK studies.

6.6 Summary

INR prolongation is prevalent following NVUGIB, identifying a group of patients with more severe bleeding and is independently and strongly associated with the subsequent risk of in-patient mortality. The importance of identifying and monitoring coagulopathy is well described in traumatic haemorrhage, and is a common feature in hospital guidelines for massive haemorrhage protocols. However, many questions remain about the extent to which findings in trauma haemorrhage can (or should) be generalised to other patient groups with major bleeding. The pathophysiology of haemostatic breakdown in patients with AUGIB bleeding might be expected to differ from trauma, as patients with AUGIB have different clinical features, mode of injury and a greater burden of co-morbidities. AUGIB represents the largest burden of major bleeding in hospitals, but further work is required to understand the mechanisms underlying development of coagulopathy and whether early interventions such as transfusion of large quantities of plasma to correct this can improve clinical outcomes.

7 Chapter Seven

Characteristics, management and outcomes of patients with liver cirrhosis and acute variceal haemorrhage

7.1 Introduction

Three decades ago, the case fatality following an episode of AVH was in the order of 40-50%, with further bleeding rates of over 30% (Graham and Smith, 1981). Since then, there have been several developments in the management of portal hypertension and variceal bleeding including early pharmacological therapy with vasopressors (Ioannou et al., 2001), use of prophylactic antibiotics (Bernard et al., 1999; Chavez-Tapia et al., 2010), emergency endoscopic therapy (Triantos et al., 2006), access to salvage therapy with transjugular intrahepatic portosystemic shunting (TIPSS) (Boyer and Haskal, 2005), as well as improvements in general supportive and critical care. Many of these interventions have been incorporated into clinical guidelines.

The first large scale UK evaluation of outcomes following AVH was conducted twenty years ago. This was a multi-centre prospective audit of acute upper gastrointestinal bleeding (AUGIB) reporting data from over 4000 cases of AUGIB from all causes, across 73 hospitals; 4% of presentations were secondary to AVH with an associated in-hospital mortality of 23% (Rockall et al., 1995). Whilst improved survival following variceal haemorrhage has been reported in several countries over the past two decades (Carbonell et al., 2004; Chalasani et al., 2003; Hobolth et al., 2010; McCormick and O'Keefe, 2001), there are few recent data available to inform practice in the UK. The UK audit provides a unique opportunity to describe modern day characteristics, process of care and outcomes in a large cohort of patients with cirrhosis and AVH.

7.2 Aims

This analysis was performed with the following objectives:

1. To describe the characteristics, processes of care (including the use of pharmacological therapy, endoscopic therapy and use of blood components) and outcomes of patients with cirrhosis and AVH, comparing these where relevant, to recommended best practice as published in clinical guidelines.
2. To make longitudinal comparisons with a previous large UK audit conducted with similar methodology in 1993 (Rockall et al., 1995);
3. To identify clinical variables associated with further bleeding and mortality;
4. To examine the utility of conventional risk stratification scores in predicting clinically important outcomes following AVH.

7.3 Methods

7.3.1 Definition of liver cirrhosis

The diagnosis of cirrhosis was recorded based upon the clinician's assessment using standard criteria including, clinical evaluation, laboratory results, radiological data or histological findings. Data were also recorded on the presence of ascites and encephalopathy, although severity grading of severity was not sought due to the inherent subjectivity in these assessments. Laboratory parameters to permit calculation of the Model for End Stage Liver Disease (MELD) score were also recorded (Kamath et al., 2001). Details recorded at endoscopy included presence of high risk stigmata of recent bleeding, as well as the type of therapeutic procedure if performed. High risk stigmata were defined as the presence active bleeding, an adherent clot, nipple sign, or fresh blood in the upper GI tract in the presence of varices. For this analysis it was decided *a priori* to only include those patients with an endoscopically confirmed

variceal source of bleeding. A pragmatic definition used in routine clinical practice was utilised for the endpoint of further bleeding, rather than formal Baveno consensus criteria for AVH (de Franchis, 2005; de Franchis, 2010).

7.3.2 Statistical methods

Logistic regression models were used to identify clinical variables associated with further bleeding and mortality. These were adjusted for a set of potentially confounding variables and potential predictors of further bleeding and mortality, selected from the literature, based upon clinical relevance amongst baseline clinical characteristics, endoscopic findings, pharmacological therapies and admission status, which were all defined *a priori* (Ben-Ari et al., 1999; Burroughs and Triantos, 2008; de Franchis, 2005; Lecleire et al., 2005; Lo et al., 2004; Thomopoulos et al., 2006).

These variables were the presence of coagulopathy at admission (defined as an INR>1.5 and/or PT> 3 secs prolonged), presenting platelet count, Hb at presentation, urea concentration on admission, age, MELD score, haemodynamic shock at presentation with bleeding, use of an anti-platelet agent (either NSAIDS, clopidogrel, aspirin, dipyridamole or SSRIs), presentation with ascites/encephalopathy, presentation out of normal working hours, in-patient status at the time of bleeding, high risk endoscopic stigmata of haemorrhage (spurting vessel, nipple on varix, adherent clot on varix, fresh blood in the upper gastrointestinal tract).

Receiver operating characteristic (ROC) curves were used to evaluate the predictive ability of the MELD score as well as the Clinical and Full Rockall scores for further bleeding, mortality, need for therapeutic intervention and need for early RBC

transfusion using SPSS version 20. For the MELD score, ROC curves were constructed only for those patients with all variables to permit calculation of the score.

7.3.3 Outcome measures

A pragmatic definition used in routine clinical practice was utilised for the endpoint of further bleeding, rather than formal consensus criteria for AVH (de Franchis, 2005; de Franchis, 2010). The definition of further bleeding in this study included any component of further haematemesis, passage of fresh melaena, continuing or recurrent hypotension and tachycardia with or without a fall in Hb after the first endoscopy. In addition to being a pragmatic definition, this was an almost identical definition to that used in the previous 1993 UK audit (Rockall et al., 1995). In hospital further bleeding and mortality, censored at Day 30 was also recorded.

7.4 Results

Of the 6,750 patients, 5004 underwent an in-patient endoscopy, of whom 526 patients with cirrhosis were found to be bleeding from an endosopically proven source of variceal haemorrhage.

7.4.1 Patient characteristics

The mean age of the cohort was 54.5 years and 68% (n=355) were male. 65% (343/526) patients who presented with AVH had a prior documented history of cirrhosis. The vast majority of bleeds were new presentations to hospital with 54% (n=287) presenting out of normal working hours and 22% (n=116) at the weekend. 55% (n=291) presented with haemodynamic shock and over one-third with other clinical signs of decompensation including ascites (34%, n=177) and encephalopathy (13%, n=69). The most prevalent co-existing morbidities were ischaemic heart disease (8%, n=40), closely followed by respiratory disease (6%, n=33) and chronic renal impairment (6%, n=31). A history of alcohol abuse was recorded in 76% (40) of patients. The median MELD score was 16 (IQR 11-20) and clinical Rockall score on admission 4 (IQR 3-5). In terms of medications which interfere with platelet aggregation and/or function, 8% (n=42) were taking regular aspirin, 8% (n=44) SSRI agents and 4% (n=22) NSAIDs ***(Table 7.1)***.

Table 7.1: Clinical and laboratory characteristics and pharmacological treatments.

All Data %(n) unless otherwise stated	**N= 526**
Baseline characteristics	
Age mean (sd)	54.5 (13.2)
Male	68 (355)
Acute admission	86 (452)
In-patient bleed	13 (69)
Pre-existing co-morbidities	
Ischaemic heart disease	7.6 (40)
CCF	2.7 (14)
Respiratory disease	6.3 (33)
Malignancy	5.1 (27)
Stroke	2.9 (15)
Chronic renal impairment	7.3 (88)
Clinical Presentation	
Shock	55 (291)
Haematemesis	72 (377)
Melaena	49 (258)
Ascites	33.7 (177)
Encephalopathy	13.1 (69)
Clinical Rockall score (Median, IQR)	4 (3-5)
MELD score (Median, IQR)	16 (11-20)
Monday-Friday 0800-1700 Other (out of formal hours)	36 (187) 62 (328)
Laboratory Parameters- first recorded	
Haemoglobin (mean, SD)	9.4 (2.4)
Platelets (median, IQR)	139 (78-178)
Urea (median, IQR)	9 (5-11)
INR (median, IQR)	1.6 (1.3-1.8)
PT (median, IQR)	23.7 (26)
Creatinine (mean, sd)	97 (80)
Bilirubin (mean, sd)	71.8 (96)
Regular Medication pre-admission	
Aspirin	8.3 (42)
Warfarin	3.6 (19)
NSAID	4.2 (22)
Clopidogrel	1.0 (5)
PPI	43.7 (230)
Pharmacological Therapy pre-endoscopy	
Antibiotics	27.4 (144)
Vasopressors	44.1 (232)
PPIs – IV or bolus infusion	56.8 (299)
Antifibrinolytics	2.1 (11)
Recombinant Factor VIIa	0.2 (1)

7.4.2 Use of pharmacological therapy at presentation with bleeding

The most frequently administered pharmacological agent following presentation with bleeding prior to the index endoscopy was an intravenous PPI which was administered to 57% (n=299), followed by vasopressors in 44% (n=232) and antibiotics in 27% (n=144); 2% (11) patients received tranexamic acid and one patient was given Recombinant Factor VIIa. In those patients with a prior documented history of cirrhosis, 53% (183/343) received vasopressors and 33% (112/343) antibiotics prior to endoscopy ***(Table 7.1)***.

7.4.3 Use of endoscopy and salvage procedures to control bleeding

Endoscopy was performed within 24 hours of presentation in 66% (n=346), with 25% (n=130) of all patients receiving endoscopy within 6 hours of presentation (Table 3). 30% (n=157) of procedures were performed out of normal working hours and 22% (n=114) of all procedures performed in clinical areas outside of the endoscopy department, the most common being the operating theatre, with a total of 14% (n=74) performed under general anaesthesia. High risk stigmata of bleeding were found in 65% (n=342) of cases, and endoscopic therapy was applied in 64% (n=339) of all procedures: 5% (n=26) had a Sengstaken tube inserted either prior to or at the index endoscopy ***(Table7.2)***. A significant desaturation of oxygen was recorded in 3% (n=16) of all endoscopy reports and aspiration pneumonia was also documented in 3% (n=15) after the index endoscopy: 4 patients subsequently underwent a TIPSS procedure and bleeding was reported to have been controlled in 3 of these procedures. In those patients with a prior documented history of cirrhosis, endoscopy was performed with 24 hours of presentation in 70% (237/343) of cases and within 6 hours in 28% (96/343) of cases.

Table 7.2: Endoscopic data, Transfusion and Clinical Outcomes

All Data % (N) unless otherwise stated	**N= 526**
No. of endoscopies	
1	69 (364)
2	25 (130)
3	5 (26)
High risk stigmata	65 (342)
Received a therapeutic Endoscopy*	64 (339)
Band Ligation	53 (289)
Sclerotherapy	8 (43)
Cyanoacrylate glue	1 (5)
Time to Index endoscopy **	
<6 hours	25 (130)
6-11 hours	20 (106)
12-23	21 (110)
24-71	19 (102)
>72	14 (72)
Endoscopy performed in/out of hours	
In hours	70 (366)
OOH	30 (157)
Location of endoscopy	
Endoscopy department	412 (78)
Emergency Theatre	75 (14)
ICU/HDU	24 (5)
ED /Ward/Other	15 (3)
Red Blood Cells	
Received RBCs during admission	73 (386)
Received RBCs within 12 hours	61 (320)
Number of RBC units received (median, IQR)	4 (3-6)
Haemobglobin prior to transfusion g/dL (mean,sd)	8.1 (6.9-9.3) g/dL
Fresh Frozen Plasma	
Received FFP during admission	35 (184)
Number of FFP units received (median, IQR)	4 (2-6)
INR before transfusion (median, IQR)	1.8 (1.2)
Prothrombin time before transfusion (median, IQR)	20.0 (6.4)
Platelets	
Received Platelets during admission	14 (76)
Number of Platelet units received (median, IQR)	2 (1-2)
Platelet count before transfusion (median, IQR)	43 (30-62)
Cryoprecipitate	7.2 (38)
Outcome Summaries	
In-hospital mortality	15.2 (80)
Further Bleeding	25.7 (135)
Length of stay in days (median, IQR)	9 (5-21)

*Information on type of therapeutic procedure not available for two patients; ** Information on primary endoscopist not available for 19 cases; † Includes all endoscopies; ‡ Data not available for the following % of cases per variable: Shock (1), Ascites/Encephalopathy (40), in-patient bleeding (1), Use of antiplatelets (10), Haemoglobin (6), Urea (11), Platelet count (7), Prolonged coagulation screen (8), HRS at endoscopy (10), MELD score (44).

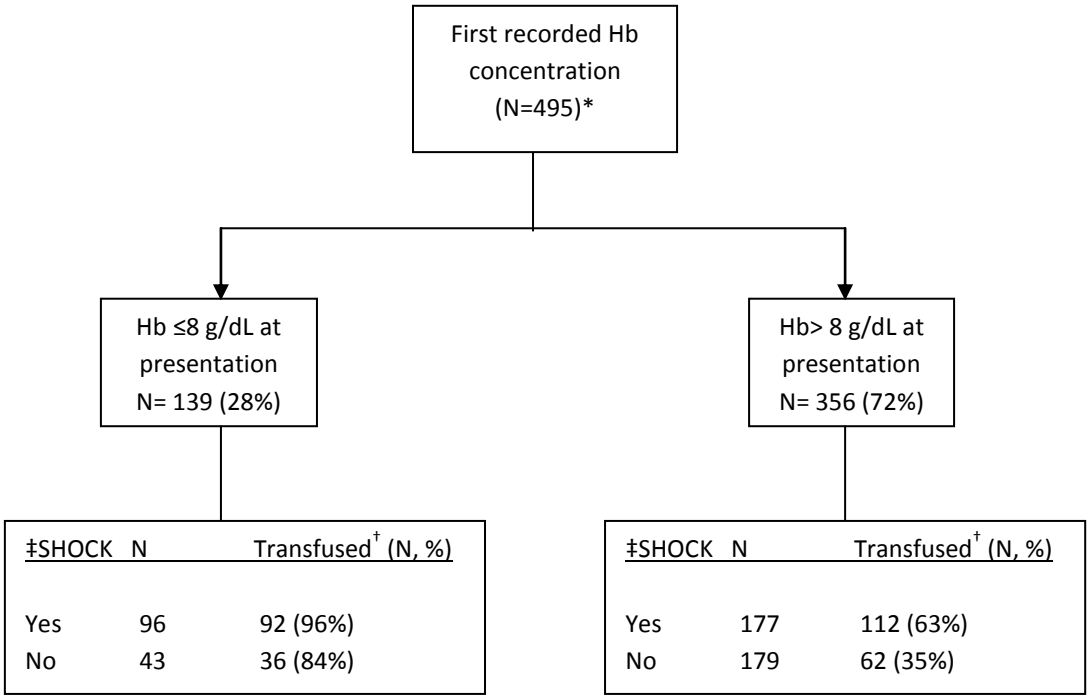
7.4.4 Use of Blood Components

The majority of patients (73%, n=386) were transfused RBCs with 61% (n=320) receiving them within 12 hours of presentation. The median Hb prior to transfusion was 8.1 g/dL (IQR 6.9-9.3) with a median of 4 units transfused in total (IQR 3-6) ***(Table 7.2)***. In patients with a presenting of Hb >8 g/dL and no evidence of haemodynamic shock, 35% (62/179) were transfused RBCs within 12 hours of presentation; conversely 37% (65/177) of patients with a presenting Hb>8 g/dL with evidence of haemodynamic shock, were not transfused RBCs within 12 hours of presentation ***(Figure 7.1)***.

FFP was transfused in 35% (184/526) of patients with a median of 4 units per patient (IQR 2-6); the median INR prior to transfusion of FFP was 1.8 (1.3-2.1) and the median PT prior to transfusion was 20 (16-22). 17% (39/235) were transfused FFP in the presence of a normal coagulation screen (INR ≤1.5 and/or PT<3 secs prolonged) whereas 41% (102/248) with an abnormal coagulation screen (INR>1.5 and/or PT<3 secs prolonged) were not transfused FFP ***(Table 7.2)***.

14% (76/526) of presentations were prescribed a median of 2 doses of platelets with a median platelet count prior to transfusion of 43 (IQR 30-62). Of those receiving platelet transfusion, 38% (29/76) had a platelet count of >50. Overall, 7% (38/526) were transfused cryoprecipitate and only 4 patients were transfused PCC ***(Table 7.2)***.

Figure 7.1: Early Red Blood Cell Transfusion according to Presenting Haemoglobin and haemodynamic status



*Complete data unavailable for 31 cases

† Refers to receipt of RBC transfusion within 12 hours of presentation with bleeding

‡Shock defined as presenting systolic BP<100 mm/Hg and/or heart rate>100 bpm

7.4.5 Clinical Outcomes and Predictors of further bleeding and mortality

Further bleeding occurred in 26% (135/526) of patients and overall case fatality was 15% (80/526) (both censored at day 30). Mortality in patients who did not have further bleeding was 7% (28/391), whereas mortality in those who suffered with further bleeding was 39% (52/135). The median length of hospital stay was 9 days (IQR 5-21) ***(Table 7.2)***.

The only pre-endoscopic patient related characteristic significantly associated with the subsequent risk of further bleeding was the presence of coagulopathy on admission (odds ratio (OR) 2.23, 95% CI 1.22 to 4.07; *P*=0.01). As expected, the presence of high risk endoscopic stigmata was also predictive of further bleeding ***(Table 7.3)***.

Clinical and laboratory characteristics most strongly associated with mortality were in-patient status at the time of bleeding (OR 7.14, 95% CI 3.45 to 14.3; *P*<0.001), the presence of ascites or encephalopathy (OR 4.18, 95% CI 1.58 to 11.06; *P*=0.004), coagulopathy (OR 3.06, 95% CI 1.29 to 7.26; *P*=0.01), fresh blood in the upper GI tract (OR 2.40, 95% CI 1.28 to 4.51; *P*=0.01) and presentation with haemodynamic shock (OR 2.10, 95% CI 1.07 to 4.13; *P*=0.03) ***(Table 7.3)***.

Table 7.3: Clinical, Laboratory and Endoscopic predictors of In-hospital mortality and Further bleeding

Variable‡	Further Bleeding		Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value
Shock	1.17 (0.73, 1.86)	0.52	2.10 (1.07, 4.13)	0.03
Ascites or Encephalopathy	1.40 (0.80, 2.44)	0.23	4.18 (1.58, 11.06)	0.004
Presentation OOH	0.99 (0.63, 1.55)	0.97	1.23 (0.64, 2.39)	0.54
In-patient bleeding	1.69 (0.92, 3.13)	0.09	7.14 (3.45, 14.3)	<0.001
Use of antiplatelet agent	0.76 (0.42, 1.36)	0.36	0.96 (0.39, 2.36)	0.93
Haemoglobin ≤8 g/dL*	1.28 (0.91, 1.78)	0.15	1.16 (0.71, 1.90)	0.55
Urea ≥12**	1.16 (0.81, 1.65)	0.42	1.01 (0.65, 1.58)	0.96
Platelet count <50***	0.91 (0.71, 1.17)	0.47	0.69 (0.50, 0.93)	0.02
Coagulopathy	2.23 (1.22, 4.07)	0.01	3.06 (1.29, 7.26)	0.01
Fresh blood in the UGIT	2.71 (1.73, 4.24)	<0.001	2.40 (1.28, 4.51)	0.01
High risk stigmata at endoscopy	1.74 (1.02, 2.99)	0.04	1.40 (0.69, 2.83)	0.35
MELD ≥18†	0.74 (0.46, 1.19)	0.21	1.61 (0.87-2.97)	0.14

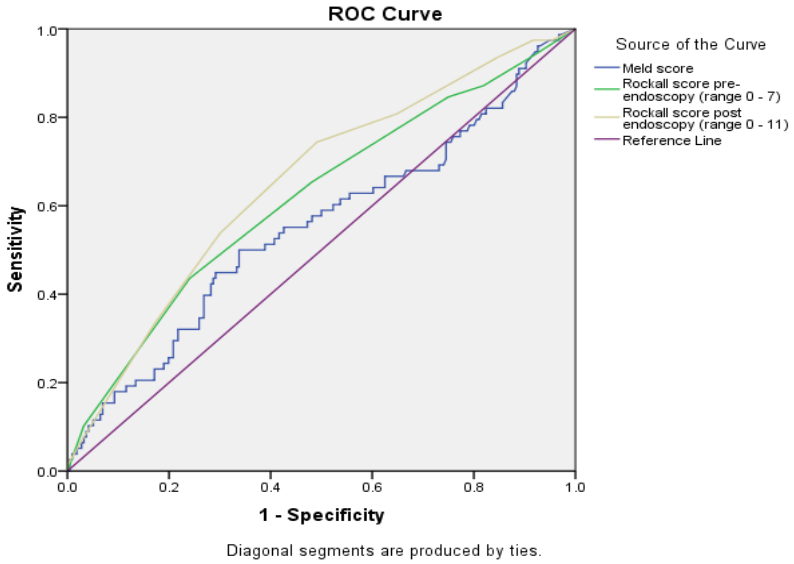
Reference categories: * Haemoglobin >8 g/dL; ** Urea <12; *** Platelet count >50; †MELD <18

‡ Data not available for the following % of cases per variable: Shock (1), Ascites/Encephalopathy (40), in-patient bleeding (1), Use of antiplatelets (10), Haemoglobin (6), Urea (11), Platelet count (7), Prolonged coagulation screen (8), Fresh blood in UGIT (0), HRS at endoscopy (10), MELD score (44).

7.4.6 Utility of Risk Stratification Scores in predicting Clinical outcome

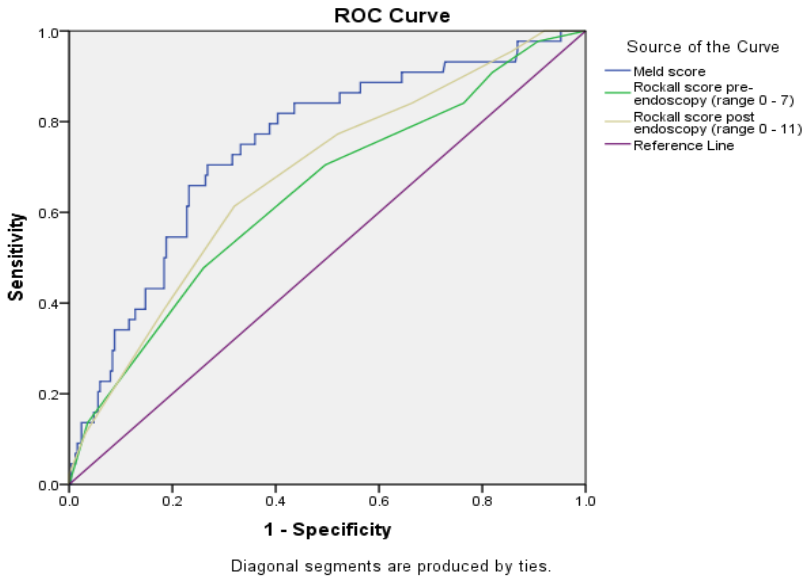
The post endoscopic Rockall score was superior to the Clinical Rockall score which was in turn superior to the MELD score in predicting the risk of further bleeding ***(Figure 7.2)***. However the area under the receiver operating curve (AUROC) for all three scores was poor. The MELD score was the best predictor of mortality (AUROC=0.74, *P*<0.001) (***Figure 7.3***). Neither the MELD nor clinical or post-endoscopic Rockall scores were useful predictors of the need for early RBC transfusion or need for therapeutic endoscopy ***(Figures 7.4 & 7.5)***. A MELD score of ≥18 further identified a group of patients at greater risk of death compared to those with a MELD <18, (unadjusted HR 3.86, 95% CI 1.95-7.67, P<0.001, compared to MELD≤18) (***Figures 7.6 & 7.7***).

Figure 7.2: Utility of the Rockall and MELD scores in predicting further bleeding



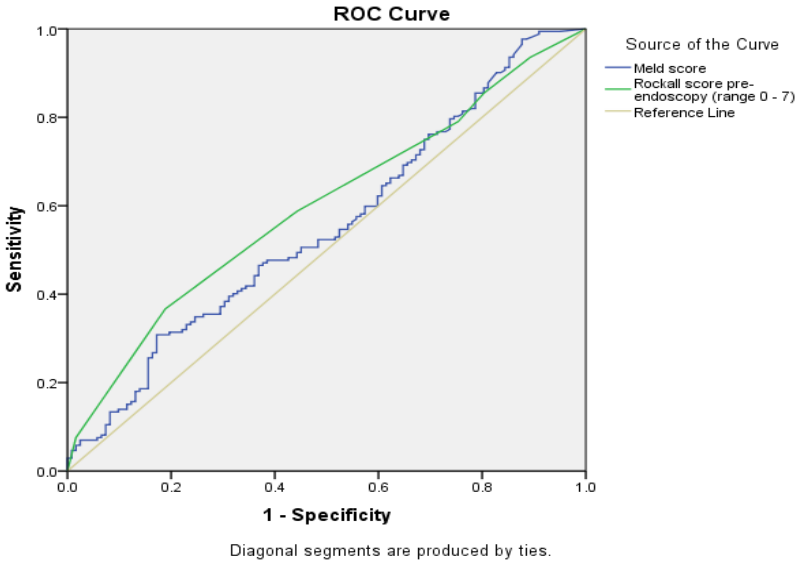
MELD: AUROC = 0.55, p=0.2
Clinical Rockall score AUROC = 0.62, p<0.05
Full Rockall Score AUROC = 0.65, p<0.01

Figure 7.3: Utility of the Rockall and MELD scores in predicting mortality



MELD: AUROC = 0.74, p<0.001
Clinical Rockall score AUROC = 0.64, p<0.005
Full Rockall score AUROC = 0.68, p<0.001

Figure 7.4: Utility of the Rockall and MELD scores in predicting need for early RBC transfusion (within 12 hours)

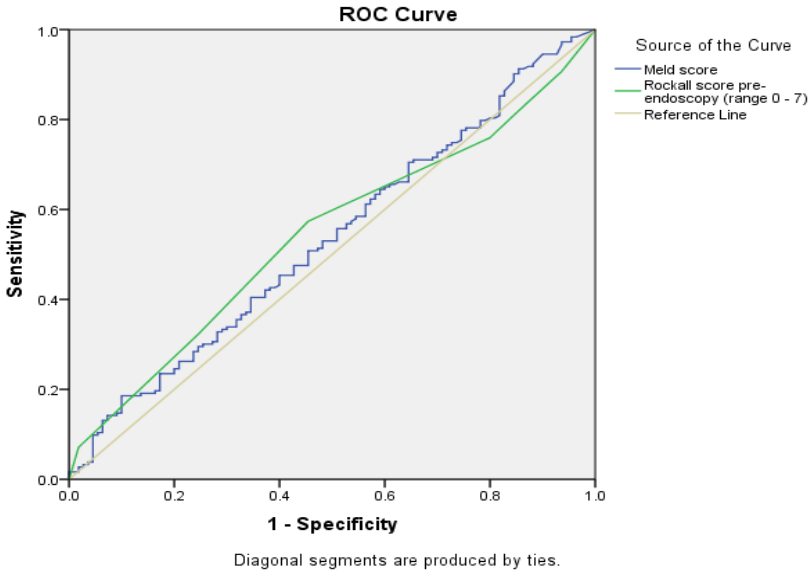


MELD: AUROC = 0.55, p<0.001

Clinical Rockall score AUROC = 0.60, p<0.005

Full Rockall score = 0.66, p<0.001

Figure 7.5: Utility of the Rockall and MELD scores in predicting use of therapeutic endoscopy

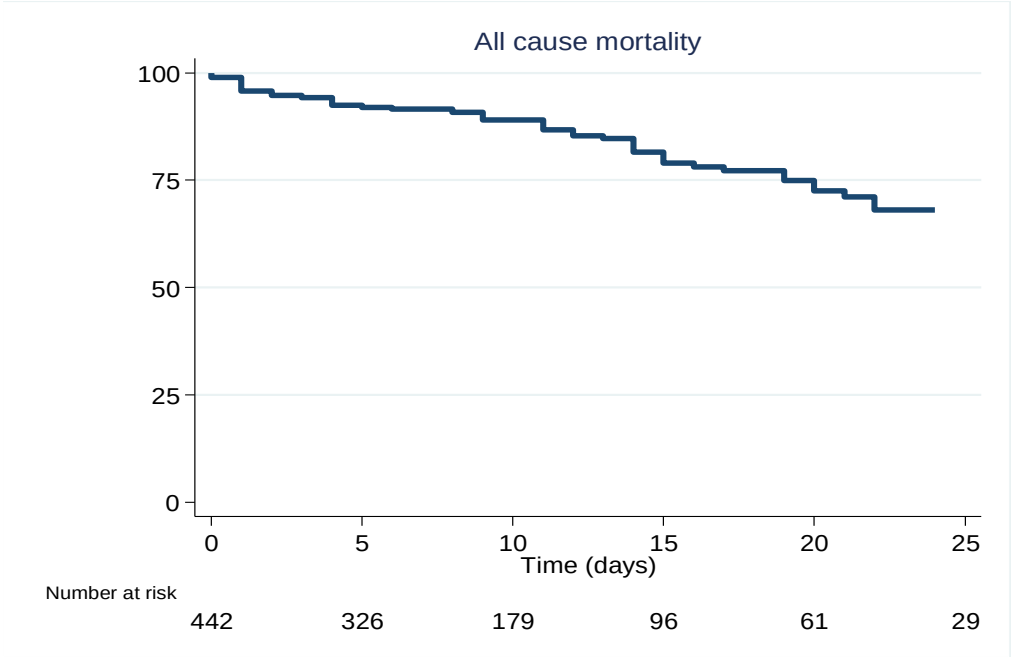


MELD: AUROC = 0.53, p=0.32

Clinical Rockall score AUROC = 0.54, p=0.31

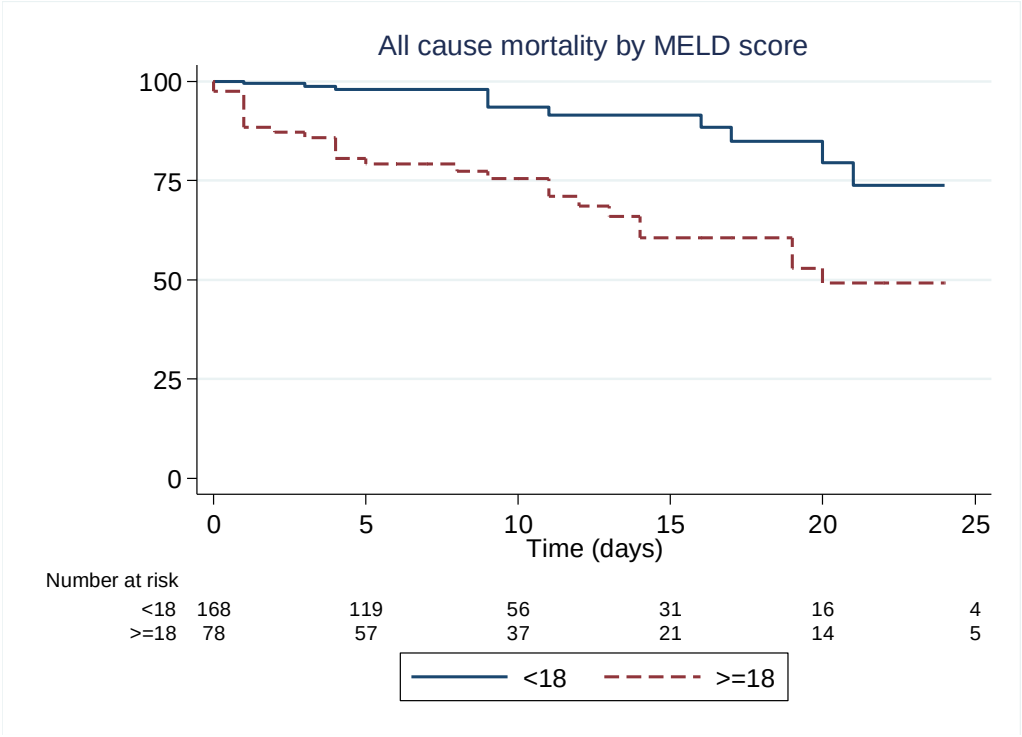
Full Rockall score= 0.69, p<0.001

Figure 7.6: Time to Death



Number at risk is 442 as time to death not available for 84 patients

Figure 7.7: Time to Death by MELD Score



Number at risk is 256 as neither MELD/ time of death available in 270 patients

7.5 Discussion

Current standards of care in the management of patients with liver cirrhosis and variceal bleeding, which also applied in 2007 when this study was conducted, include administration of vasoactive drugs and antibiotics from admission, prompt endoscopy ideally within 12 hours of presentation and endoscopic therapy, in any patient with oesophageal varices as the cause of bleeding (de Franchis, 2005; de Franchis, 2010). It is notable that only 27% of patients were given antibiotics at first presentation prior to endoscopy and 44% vasopressors, with only 49% then having a vasopressor either continued or started after endoscopy had confirmed a variceal source of bleeding. Even in those patients with a documented history of prior cirrhosis, the proportion of patients receiving vasopressors and antibiotics was only marginally higher, even though there would have been a high suspicion of a variceal source of bleeding in this group at first presentation. It is surprising that 57% of patients received intravenous PPIs prior to endoscopy given that there is no evidence they are associated with improvements in clinical outcome, in contrast with the lack of provision of prophylactic antibiotics which have been shown to confer up to a 20% reduction in all cause mortality and 50% reduction in further bleeding following AVH (Chavez-Tapia et al., 2010).

Only two-thirds of patients had an endoscopy performed within 24 hours of presentation. Deficiencies in the timely provision of endoscopy in the UK have been previously described (Hearnshaw et al., 2010) and have led to national initiatives to address shortcomings in provision of 24 hour access to endoscopy. It will be important to monitor these improvements in future longitudinal studies. Whilst there is some evidence that endoscopy within 12 hours may confer a survival benefit in patients with active variceal bleeding (Chen et al., 2012), more work is needed in this area, similar to

evidence from patients with NVUGIB, with detailed adjustment for potential confounding variables (Jairath et al., 2012).

The last few years have seen an exponential increase in reports describing mechanisms and strategies for acute resuscitation following major haemorrhage, including the identification of acute traumatic coagulopathy and the early use of plasma which is considered to improve outcomes following traumatic haemorrhage. Although this study suggests that coagulopathy (defined as an INR>1.5 and/or a PT> 3 secs prolonged) is strongly associated with further bleeding after AVH, this does not necessarily indicate that targeted management of coagulopathy will be effective in reducing further bleeding, which requires a better understanding of the pathophysiology and interventional trials. Early and aggressive transfusion of plasma, if extrapolated from other clinical models of major haemorrhage, may risk further exacerbation of portal hypertension with excessive volume replacement, and there is evidence that early failure to control bleeding is 4 times greater in patients with HVPG> 20mm Hg than in patients with a HVPG<20 mm Hg (Abraldes et al., 2008). Both Baveno IV (de Franchis, 2005) and V (de Franchis, 2010) guidance state that no recommendations can be made regarding the management of coagulopathy and thrombocytopenia in patients with portal hypertension and variceal bleeding given a lack of research. Further research needs to assess haemostatic balance in patients not only with stable liver disease using global tests of coagulation such as thrombin generation (Gatt et al., 2010; Tripodi and Mannucci, 2011) but also in patients with AVH.

The optimum use of RBCs following AUGIB is also controversial (Hearnshaw et al., 2010; Jairath et al., 2011; Jairath et al., 2010). At the time this study was conducted there was evidence from rodent studies (Castaneda et al., 2001) then followed by

provisional data from a RCT suggesting a more liberal approach to transfusion may be associated with a greater risk of further bleeding due to exacerbation of hepatic venous pressure gradient (HVPG) (Colomo A, 2008). This has now been confirmed in an RCT which provides a stronger evidence base for consensus guidelines which recommend a restrictive approach to RBC transfusion at a Hb target of 7-8 g/dL (Villanueva et al., 2013). In the present study, 73% of patients received RBC transfusion with some evidence of a more liberal approach to transfusion; for example 35% patients with a presenting Hb>8g/dL with no evidence of haemodynamic shock received RBC transfusion within 12 hours of presentation. Longitudinal studies will be required to assess how well this new evidence translates into a more restrictive transfusion practice in a real-life setting.

Clinical variables strongly associated with mortality were inpatient status at the time of bleeding and the presence of ascites or encephalopathy; whilst these support previous findings (Ben-Ari et al., 1999; D'Amico and De Franchis, 2003) they serve to remind us that many patients with cirrhosis die due to severity of underlying liver disease as opposed to severity of bleeding per se, with bleeding initiating a train of downstream events despite achieving adequate control of haemorrhage (Burroughs and Triantos, 2008). However, mortality in those patients who suffered with further bleeding was more than five-fold (39% vs. 7%) greater than those patients who did not; thus prevention of further bleeding, arguably the best outcome measure resulting from interventions directly targeted at arresting haemorrhage, should be a key goal in the management of AVH. The further bleeding rates reported in this study are appreciably higher than those from studies conducted during a similar timespan (Bambha et al., 2008; D'Amico and De Franchis, 2003), for reasons that are unclear but may reflect differences in the use of pharmacological agents, endoscopic therapy, case mix and

definitions. As with NVUGIB, improvements in further bleeding should be a key goal in new research.

Use of risk stratification scores to predict clinical outcome are well established in the setting of NVUGIB and their routine use has obvious clinical benefits (Jairath and Barkun, 2012). This study demonstrates that neither the clinical nor full Rockall scores are good predictors of clinical outcomes following AVH. The MELD score was a statistically significant predictor of mortality, but not of further bleeding, with an AUROC for mortality similar to those reported in two previous studies (Amitrano et al., 2005; Chalasani et al., 2002). However, an AUROC of 0.74 for mortality is not a strong prediction tool and there is the need for a new, simpler score to better predict outcomes following AVH which can both account for severity of bleeding and underlying liver disease. Abraldes and colleagues have previously identified a simple clinical prediction rule for failure to control bleeding (Abraldes et al., 2008), although we were unable to validate this in the present study due to absence of information on aetiology of cirrhosis. Similar to a study in the US, which used data from an RCT in which all patients received strict protocols of care (Bambha et al., 2008), we found that a MELD>18 still identified a group of patients at especially high risk of death following AVH, even though care was not protcolised in the current study.

The strengths of this study include its large sample size, detailed description of clinical characteristics and nationwide geographical location of participating units suggesting the population studied was generalisable. Limitations include the secondary analysis of prospectively collected data and the potential for unrecognised confounding variables in the regression analysis, given this was an observational study. Insufficient data was available to permit calculation of the MELD score in 40% of cases and it is possible that

these data may have altered the predictive value of the MELD score in these analyses. Whilst direct comparisons with the 1993 UK audit of AUGIB where mortality following AVH was 23% (Rockall et al., 1995) compared to 15% here will inevitably be made, it is important to recognise that there were some differences in study methodology. The 1993 study covered 73 hospitals in four healthcare regions, whereas the more recent audit was a nationwide assessment with a greater number of cases, centres and more detailed data capture. Whilst there are some limitations to analyses derived from Hospital Episode Statistics (HES) in England, mainly due to concerns in accuracy of clinical coding, the reduction in mortality observed in the period between these national two audits in patients with variceal bleeding is supported by a recent study using HES data in England (Crooks et al., 2011), lending further support to the trends reported in the current study and the methodology of case ascertainment.

7.6 Summary

Whilst UK mortality following AVH has reduced since the last large scale evaluation in 1993, further bleeding rates remain high. There are notable shortcomings in following evidence based practice mainly in terms of early use of vasopressors and timely use of endoscopic therapy. Further research is needed to understand the appropriate use of blood components following variceal haemorrhage, the value of correcting coagulopathy, together with the need for development of a simple risk stratification score to better predict outcomes following AVH.

8 Chapter Eight

Evaluation of haemostatic derangements in acute variceal haemorrhage and implications for treatment

8.1 Introduction

In Chapter 7, the variable use of blood components for the management of AVH in patients with liver cirrhosis was noted. The evidence base for the use of RBCs following AVH is improving and the risks of injudicious transfusion have been highlighted in an RCT of RBC transfusion strategies, where more liberal transfusion was associated with excessive further bleeding rates, which was postulated due to a direct effect on portal pressure with more liberal transfusion (Villanueva et al., 2013). Prohaemostatic blood components such FFP, platelets and cryoprecipitate are frequently transfused as part of initial resuscitation in response to abnormal standard laboratory coagulation indices, although there is no evidence base to guide their use as is acknowledged in expert consensus guidelines (de Franchis, 2005; de Franchis, 2010).

A better understanding of which components of the coagulation cascade become abnormal during AVH would facilitate a more targeted and rational approach to transfusion and use of haemostatic agents (Jairath and Burroughs, 2013). This is important both to facilitate control of bleeding and potentially the prevention of further bleeding, and to avoid the risks associated with unnecessary over or under-transfusion. This would also provide data required for the design of new interventional studies to evaluate pro-haemostatic transfusion strategies in patients with variceal bleeding.

8.2 Aims

The aims of this study were:

1. To characterise the derangements in global haemostasis in patients with cirrhosis at the point of presentation with AVH using thrombin generation tests and thromboelastometry (ROTEM), as well defining levels of individual coagulation factors, fibrinogen and platelet counts.
2. To determine in an *ex vivo* model whether administration of fibrinogen concentrate (FgC), platelets, FFP, prothrombin complex (PCC) or antifibrinolytics lead to improvements in the haemostatic profile of bleeding patients as measured by thromboelastometry.

8.3 Methods

8.3.1 Patient selection

Consecutive adult cirrhotic patients presenting with haematemesis and/or melaena to the Emergency Department (ED) of a university teaching hospital were enrolled. Adult patients with stable cirrhosis attending a hepatology outpatient clinic formed a control population and were matched according to disease severity by Child-Pugh score. The only exclusion criteria were patients taking warfarin, other anticoagulants, antifibrinolytics or other known (congenital) haemostatic disorders. The study was approved by the National Research Ethics Committee, under the Mental Capacity Act for England 2005 (REC reference 10/H0709/14; Appendix A).

The accurate assessment of global haemostasis at the point of presentation with acute haemorrhage requires blood sampling before transfusion of blood components or large quantities of fluids, which will confound the results of the assays. In the context of AVH, this represents a logistical challenge, since around two-thirds of patients with

AUGIB present out of normal working hours in the UK, and infusions of blood components and intravenous fluids starts shortly after presentation to hospital as part of resuscitation. To facilitate early capture of blood samples, the ED and Blood Bank staff telephoned me on presentation of a suspected variceal bleed at any time of day. This was made possible through regular attendance to the ED to present the purpose of the study to doctors and nurses at clinical handovers, presentations to the gastroenterology department and daily phone-call to the registrar on-call, regular liaison with blood bank staff and through information posters for staff in emergency areas with my contact details.

In patients presenting with AUGIB, a 20ml research sample of blood was drawn on first arrival to the ED. Patients were then approached, appropriate to their clinical condition, to seek written informed consent for testing of blood samples already drawn. The diagnosis and aetiology of cirrhosis was confirmed upon standard clinical, laboratory and ultrasound evidence. Severity of cirrhosis was calculated according to both the Child-Pugh (Pugh et al., 1973) and model for end stage liver disease (MELD) classifications (Kamath et al., 2001). Results for endoscopy were documented, including the source of variceal haemorrhage. Patients were followed up until discharge, up to a maximum of 28 days.

8.3.2 Blood sampling and plasma preparation

Blood was drawn into vacutainer tubes (Beckton, Dickinson, Oxford, UK) containing 105 mmol/L trisodium citrate (1:9, anticoagulant:blood). All samples were transported upright to the research laboratory and processed within 60 minutes of collection. Blood for rotational thromboelastometry analysis was processed on whole blood. For the remaining samples, platelet poor plasma (PPP) was obtained by a centrifugation at

2000g for 20mins at room temperature, followed by high speed centrifugation at 13,000g for 2 minutes to eliminate platelets. Plasma supernatants were separated without disturbing the platelet pellet after each centrifugation step. After analysis, the platelet free plasma was stored at -80^{0}C until analysis.

8.3.3 Routine coagulation tests and factor assays

Peripheral blood counts, liver function tests and markers of infection in bleeding patients (including white cell count, CRP, cultures of blood/urine/ascites/stool where applicable) were all recorded as per routine care. Fibrinogen was measured using the Clauss method (Clauss, 1957). The prothrombin time (PT) and activated partial thromboplastin time (APTT) were performed by a mechanical optical method on an automated coagulation analyser (STA-R Evolution Analyser®, Stago).

All coagulation factors were measured using conventional one-stage methods over multiple dilutions on the STA-R Evolution Analyser®. The procoagulant factors measured include factors II, V, VII, VIII, IX, X, XI. Factors II, V, VII, and X were determined by performing a modified PT assay and factors VIII, IX and X by performing a modified APTT assay. Anticoagulant factors measured include protein C, protein S and antithrombin. Protein C activity was measured by the synthetic chromogenic substrate method (STA®- Stachrom® protein C, Diagnostica Stago) and free protein S antigen by an antigenic assay using an immuno-turbidimetric method (STA® – Liatest® free protein S, Diagnostica Stago). Antithrombin activity was measured using a colorimetric assay by the synthetic chromogenic substrate method (STA®- Stachrom® ATIII, Diagnostica Stago). Levels are provided as percentages relative to normal pooled plasma.

8.3.4 Rotational thromboelastometry (ROTEM) analysis:

ROTEM is a device which measures the viscoelastic properties of coagulation in whole blood within minutes, including the speed of coagulation initiation, kinetics of clot growth, clot strength and breakdown (fibrinolysis). The methodology has been previously described in detail (Ganter and Hofer, 2008). Briefly, each channel of the device consists of a vertical axis, held by a ball-bearing system and connected by wire spring to a motor, which rotates the axis continuously through a 4.76^0 angle ***(Figure 8.2)***. A disposable plastic pin is attached at the lower end of the axis and a disposable cup containing whole blood is placed under the axis. As blood begins to coagulate, fibrin strands and platelet aggregates become attached to the pin and obstruct the axis movement. The software converts the rotational amplitude of the axis into clot firmness or amplitude, to produce a graphical plot over time (60 mins) ***(Figure 8.3).***

In this study samples were processed within 60 minutes of blood draw using a ROTEM delta instrument (TEM International GmbH, Munich, Germany) at 37°C. The device was tested monthly using quality control serum (ROTROL, Pentapharm GmbH). Three separate ROTEM assays were performed for each patient:

1. EXTEM test measuring tissue factor initiated coagulation reflecting extrinsic activation of coagulation (20UL CaCL2 0.2 mol/L, 20L tissue factor, 300Ul blood).
2. FIBTEM test, with the addition of cytochalasin D, a platelet inhibitor, reflects the contribution of fibrinogen to clot formation (20UL CaCL2 0.2 mol/L, cytochlasin D, 20UL tissue factor, 300Ul blood).

3. APTEM test which involves addition of a fixed quantity of the antifibrinolytic drug Aprotinin, an inhibitor of plasmin, to determine if coagulation can be improved in the presence of fibrinolysis.

The following ROTEM parameters were measured ***(Figure 8.3)***:

1. Clotting time (CT), representing the time from the start of the analysis until the clot strength is 2mm and measures the initiation of coagulation, which is determined by levels of coagulation factors.
2. Clot formation time (CFT), which is the time from the start of coagulation until the clot strength is 20mm, reflecting the rate of clot formation, reflecting fibrin polymerisation through the interaction between fibrin and platelets.
3. Alpha angle, which reflects the kinetics of clot formation, measuring the rate of fibrin formation and cross-linkage.
4. Maximum clot firmness (MCF), which measures the maximum strength of the clot, contributed to mainly by platelets and fibrinogen.
5. Maximum lysis (ML), representing the maximum fibrinolysis detected during the 60 minute assay time, defined as the ratio of the lowest amplitude after reaching of the MCF and the MCF (Lang et al., 2005); an ML>10% indicates fibrinolysis and a trigger at which antifibrinolytics would be commonly be administered in clinical practice in patients with haemorrhage.
6. LI60, the lysis index at 60mins, representing the % of the MCF remaining at the end of 60 mins. Reference ranges for the tests' parameters have been previously determined in a multi-centre investigation (Ganter and Hofer, 2008).

Figure 8.1: Cross-sectional view of ROTEM channel

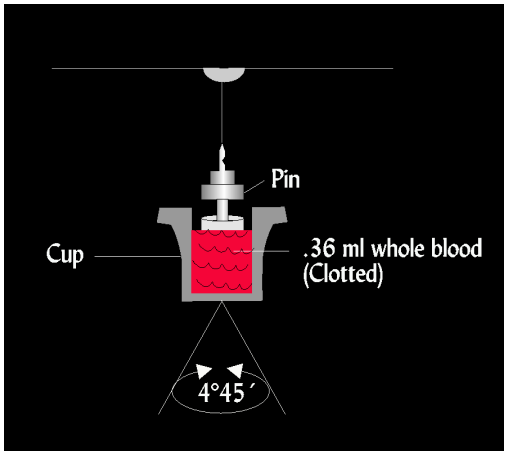
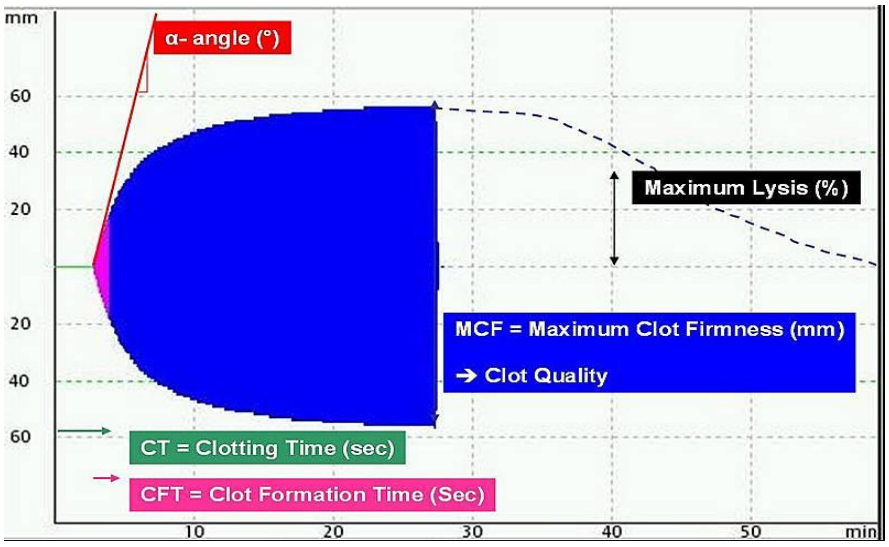


Figure 8.2: Main parameters of a ROTEM output



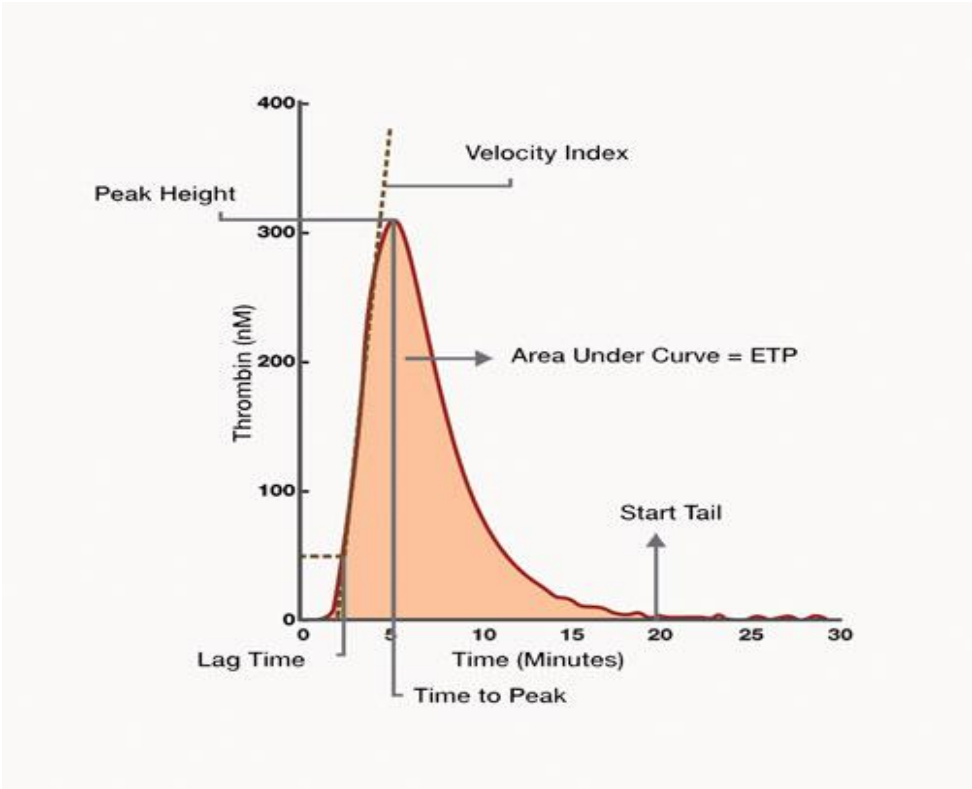
8.3.5 Thrombin generation (TG)

Whilst routine coagulation assays such as the PT or APTT are useful for the detection of coagulation factor deficiencies and the biological monitoring of the effects of coumadins and unfractionated heparin, they are otherwise crude and static indices sensitive only to the effect of procoagulant factors and insensitive to anticoagulant factors. At the time of clot formation in a PT test, only 3% of prothrombin is activated (Mann et al., 2003), so it does not accurately reflect the process of TG, which explains why it is a poor predictor of bleeding or thrombosis. TG assays measure the dynamics of all phases of TG (initiation, amplification, inhibition and total amount of thrombin generated) using small amounts of tissue factor as a trigger to achieve a full interplay of all coagulation factors. Whilst TG assays are predominantly utilised in a research setting, increasing sophistication and automation are likely to translate into greater clinical use, since they have already been shown to be useful in identifying patients at increased risk of thrombosis (Besser et al., 2008) and bleeding (van Veen et al., 2008).

8.3.5.1 Calibrated automated thrombogram

In this study, TG was assessed by calibrated automated thrombinography (CAT) as described by Hemker *et al.* (Hemker et al., 2003). This method utilises a low affinity substrate for thrombin (Z-Gly-Gly-Arg-AMC) to continuously monitor thrombin activity in plasma. Several parameters of the curve were measured including: (1) Lag time (LT), representing the time to initiation of thrombin formation; (2) Peak height (Peak), representing the maximum amount of thrombin generated; (3) Time to peak (ttPeak) thrombin generation; (4) Endogenous thrombin potential (ETP), representing the total amount of thrombin generated during the test (area under the curve) ***(Figure 8.4)***.

Figure 8.3: Parameters of the thrombin generation curve as evaluated by calibrated automated thombinography



8.3.5.2 Dose of Tissue Factor to trigger TG

There are conflicting data in the literature regarding whether a higher or lower concentration of tissue factor (TF) should be used to trigger TG. Although a lower concentration of TF is thought to be more physiologically representative, there is also evidence that lower concentration of TF result in erroneously high TG, as this makes the test more prone to the *in vitro* activation of the contact system occurring during blood drawing or blood storage (Dargaud et al., 2006; Dargaud et al., 2012). Recognising that previous studies examining TG in patients with liver disease have also used differing concentrations of tissue factor (TF) to trigger TG (Agarwal et al., 2012; Gatt et al., 2010; Tripodi et al., 2009), (i.e. both high and low tissue factor concentrations) I ran a test plate of parallel samples using a higher TF concentration (5pM; PPP reagent, Thrombinoscope, BV) and at lower TF concentration (1pM; PPP-low reagent, Thrombinoscope, BV). Since no statistically significant difference was observed in any parameter of the curve (data not shown), I completed the experiments using the higher concentration of TF to initiate TG (5pM; PPP reagent, Thrombinoscope, BV) as per similar studies measuring TG in patients with stable cirrhosis and acute liver failure.

To correct for inner filter effects and substrate consumption, each TG measurement was calibrated against the fluorescence curve obtained in the same plasma with a fixed amount of thrombin-alpha 2-macroglobulin complex (Thrombin Calibrator, Thrombinoscope BV). Fluorescence was continuously monitored within a Fluoroscan Ascent plate reader (Thermo Labsystems, Helsinki, Finland) with an excitation filter at 390nm and an emission filter at 460 nm. Readings from the fluorometer were generated and converted by the manufacturer's software (Thrombinoscope BV, Maastricht, The Netherlands) to derive the thrombogram.

8.3.5.3 Protac® modified thrombin generation assay

To ensure activation of the reduced levels of protein C known to occur in cirrhosis, and to account for the fact that thrombomodulin is endothelial bound *in vivo* and not free in plasma, a modified TG assay was performed in a second aliquot of plasma by adding to the test system Protac® (PentaPharm, Basel, Switzerland), a single chain glycoprotein isolated from the venom of the copperhead snake *Agkistrodon contortrix*, which is a non-physiological activator of protein C, using methods as previously described (Gatt et al., 2007; Gatt et al., 2010). The Protac® method has been validated and shown to be comparable to the thrombomodulin method of in-vitro TG testing (Agarwal et al., 2012; Gatt et al., 2007; Gatt et al., 2010; Tripodi et al., 2010).

To ensure an optimum dose of Protac® was used, the dose of Protac® was titrated to select a dose which resulted used in approximately 50% reduction in the ETP in samples from a group of healthy controls, as per previous methodology. Corn Trypsin Inhibitor was not used to inhibit contact activation either in blood collection tubes or in assay wells, since we utilised a higher concentration of tissue factor to trigger coagulation (Gatt et al., 2007; Spronk et al., 2009). All samples were handled and TG assays performed by a single operator (myself). In order to minimise variation, equal numbers of samples from patients and controls were included on each test run.

8.3.6 *Ex vivo* evaluation of blood component replacement therapies

Ex vivo analysis of the response to replacement therapy with several pro-haemostatic agents was performed on admission whole blood samples from patients with AVH. These include:

1. FFP (contains all coagulation factors at normal plasma levels).
2. Prothrombin complex concentrate (PCC- contains procoagulants II, VII, IX, X and anticoagulants C&S).
3. Platelets.
4. Fibrinogen concentrate (FgC).
5. Antifibrinolytic drug (Aprotinin, APTEM test).

Citrated whole blood samples were analysed by ROTEM after the *ex vivo* addition of two different doses of each component, except aprotinin which was a single dose. The spiking protocol has been previously described and validated (Rourke et al., 2012). For PCC, FFP and FgC, aliquots were pre-prepared (using the same vial/bag) and frozen, then thawed in a water bath at 37°C when needed and whole blood was added and mixed thoroughly. Platelets were obtained from research laboratories when an acutely bleeding patient was enrolled. Analysis of each sample was performed within 2 hours of blood draw using EXTEM & FIBTEM channels and run for 1 hour at 37°C.

The two FgC (Bio Products Laboratory, Hertfordshire, UK) doses were selected to be equivalent to administering 6g and 12g fibrinogen concentrate to a 70kg person. Assuming a 5 litre blood volume, a 6g dose reaches a final blood concentration of 1.2mg/ml and a 12g dose 2.4mg/ml; therefore the volumes of FgC added to 700µl of blood were: 14µl and 28µl for the low and high FgC doses, respectively. The two doses (6g and 12 g) were selected based on pilot data using a dilutional model of

coagulopathy, where whole blood from ten healthy volunteers was diluted 1:1 with Ringer's Lactate (Curry NS, 2011). ROTEM responses to escalating concentrations of fibrinogen, 0.6mg/ml up to 2.4mg/ml were tested to determine which concentrations showed significant reversal of the effects of dilutional coagulopathy on ROTEM.

The standard dose of PCC (CSL, Behring) was chosen to reflect clinical practice in the UK. The standard dose 25 units/kg is the most frequently used dose for adult patients with major blood loss. Assuming a 70kg person with a 5 litre blood volume, this standard dose equates to the addition of 98µl of PCC to a 700µl volume of whole blood. The high dose of PCC was chosen as double that of standard, and 196µl was added to 700µl of whole blood.

The standard dose of FFP (NHSBT, UK) was chosen to reflect clinical practice in the UK of 15ml/Kg (http://transfusionguidelines.org.uk; O'Shaughnessy et al., 2004). Assuming a 70kg person with a 5 litre blood volume, this standard dose equates to the addition of 147µl of FFP to a 700µl volume of whole blood. The high dose FFP was chosen as double that of standard (30ml/Kg), and 294µl was added to 700µl of whole blood.

The standard dose of platelets (NHSBT, UK) was chosen to reflect clinical practice in the UK i.e. one adult therapeutic dose (ATD) and the high dose was chosen as two ATDs. One ATD of platelets contains $2.5\text{-}3x10^{11}$ platelets/pool in an approximate volume of 200ml (http://transfusionguidelines.org.uk). Assuming a 70kg person with a 5 litre blood volume, this standard dose equates to the addition of 28µl of platelets to a 700µl volume of whole blood. The high dose was chosen as double that of standard (i.e. two ATDs), equating to the addition of 56 µl of platelets to a 700µl volume of whole blood.

8.3.7 Statistical Methods

Data were inspected for normality, with parametric data expressed as a mean and standard deviation and non-parametric data as a median and interquartile range (IQR). Parametric data was compared using a t-test and non-parametric data using a Mann-Whitney *U* test, with p-values of <0.05 taken a statistically significant. For spiking experiments, a paired test was used to compare ROTEM parameters before and after spiking. In order to identify independent laboratory predictors of overall maximum clot firmness (EXTEM MCF) on ROTEM, a stepwise multiple linear regression model was built. Variables included in the model were specified *a priori* and were Hb, fibrinogen level, platelet count, albumin, urea, bilirubin as well as individual pro-coagulant (II, IV, V, VI, VII-XI, XIII) and anti-coagulant factors (proteins C and S, antithrombin). Variables were retained in the model when $p<0.05$.

8.4 Results

8.4.1 Clinical characteristics

20 cirrhotic patients with AVH (mean age 55.9±16.1 yrs; 60% male) were enrolled and 43 patients with stable cirrhosis (57.4±12.6 yrs; 65% male), well matched for age, gender and aetiology of cirrhosis ***(Table 8.1)***. In both groups the predominant aetiology was alcoholic liver disease (70% vs. 63% in bleeding versus non-bleeding patients). No patient received any blood component (including RBCs, platelets, FFP, cryoprecipitate, fibrinogen or vitamin K) prior to blood sampling. All were confirmed to have bled from varices at endoscopy. Twenty eight healthy volunteers were used for comparative TG analysis and for ROTEM reference ranges.

Table 8.1: Demographic and clinical characteristics of non-bleeding and bleeding cirrhotics and controls

	Bleeding cirrhotics (n=20)	Non-Bleeding cirrhotics (n=43)	Normal ranges
Demographics			
Age (mean,sd)	55.9 (16.1)	57.4 (12.6)	-
Male % (n)	60 (12)	65 (28)	-
Aetiology %(n)			
Alcohol	70 (14)	63 (27)	-
NAFLD	5 (1)	7 (3)	-
HBV/HCV	5 (1)	19 (8)	-
Other	20 (4)	12 (5)	-
Laboratory parameters (mean, sd)			
Haemoglobin g/dL mean (sd) *	8.9 (1.6)	12.2 (2.3)	13.0-17.0
Haematocrit mean (sd) *	0.27 (0.03)	0.37 (0.06)	0.40-0.50
Platelets median (iqr) 10^9/L *	88 (42)	133 (72)	150-400
Creatinine median (iqr)mg/dL)	70 (25)	68 (37)	54-145
Albumin g/L mean (sd) *	29.5(5.3)	34.0 (7.1)	35-50
Bilirubin mg/dL mean (sd) *	86.2 (132.6)	39.2 (43.4)	3-17
ALT IU/L median (iqr)	46.2 (50.3)	35.8 (23.7)	10-45
Coagulation parameters			
PT (s) mean (sd) *	20.9 (3.9)	15.5 (2.0)	13.0-15.0
APTT (s) mean(sd)	40.1 (9.8)	36.8 (6.9)	26.0-36.0
Fibrinogen g/L median(iqr) *	1.9 (0.5)	2.6 (0.8)	1.5-4.0
D-dimer median(iqr)	3037 (1571)	2673 (3306)	<250
Child-Pugh Score %(n)			
Child-Pugh Class B C	 55 (11) 45 (9)	 60 (26) 40 (17)	 - -

* = p<0.05 for comparison of value in bleeding cirrhotics vs. non-bleeding cirrhotics.

8.4.2 Markers of infection in cirrhotics with bleeding

The median C-reactive protein level was 10.3 (IQR 22.2) and median white cell count was $10.7x10^9$/L (IQR 6.68). Two patients had positive growth in blood culture bottles at 5 days post-incubation (*Streptococcus Milleri* in one case, C*oagulase negative staphylococcus* in the other) and one patient had overt evidence of spontaneous bacterial peritonitis in ascitic fluid (>250 polymorphonuclear leucocytes/mm^3). All stool cultures, urine cultures and nasal screens were negative.

8.4.3 Coagulation results

8.4.3.1 Standard coagulation tests

In cirrhotics with AVH there was a higher PT (20.9s vs. 15.5s, p<0.01), lower Hb (8.9g/dL vs. 12.2g/dL, p<0.01), lower platelet count (88 vs. 133, p=0.01) and lower fibrinogen (1.9 vs. 2.6, p=0.005) in comparison to non-bleeding patients respectively ***(Table 8.1).***

8.4.3.2 Pro- and anti-coagulant factor levels in bleeding and non-bleeding patients

In cirrhotics with AVH, the only significant reduction in levels of pro-coagulant factors compared to non-bleeding cirrhotics was for factors VII (38.6% vs. 66.2%, p=0.02) and X (49.0% vs. 69.2%, p=0.02); the remaining levels of all other pro-coagulant factors was the same. Conversely, levels of factor VIII were highly elevated in cirrhotics with AVH compared to those without bleeding (306.0 vs. 213.7, p<0.01). Although levels of the anticoagulants proteins C & S and antithrombin were lower in patients with bleeding, none of these differences were significant ***(Table 8.2).***

Table 8.2: Levels of pro- and anticoagulant factors in bleeding and non-bleeding patients

Coagulation factor	Bleeding cirrhotics (n=20)	Non-Bleeding cirrhotics (n=43)	Reference ranges
Procoagulant factors			
II	57.9 (17.4)	63.1 (21.6)	70-120
V	63.0 (25.4)	73.0 (30.1)	70-120
VII	38.6 (18.4)*****	66.2 (36.3)	55-170
VIII	306.0 (96.0)*****	213.7 (71.0)	50-150
IX	74.6 (23.1)	78.2 (27.8)	60-150
X	49.0 (12.9)*****	69.2 (26.8)	70-120
XI	53.4 (22.0)	44.6 (17.3)	60-150
XIII	63.6 (22.2)*****	92.6 (52.7)	
vWF	354.7 (63.9)	334.9 (108.2)	
Anticoagulant factors			
Protein C	40.9 (20.2)	44.7 (21.9)	70-130
Protein S	80.5 (38.3)	90.5 (27.3)	60-140
Antithrombin	55.4 (15.9)	56.9 (22.7)	80-120

* $p<0.05$ for comparison of value in bleeding cirrhotics vs. non-bleeding cirrhotics.

All values expressed as mean (sd)

8.4.3.3 Thrombin generation in platelet poor plasma in the absence and presence of Protac®

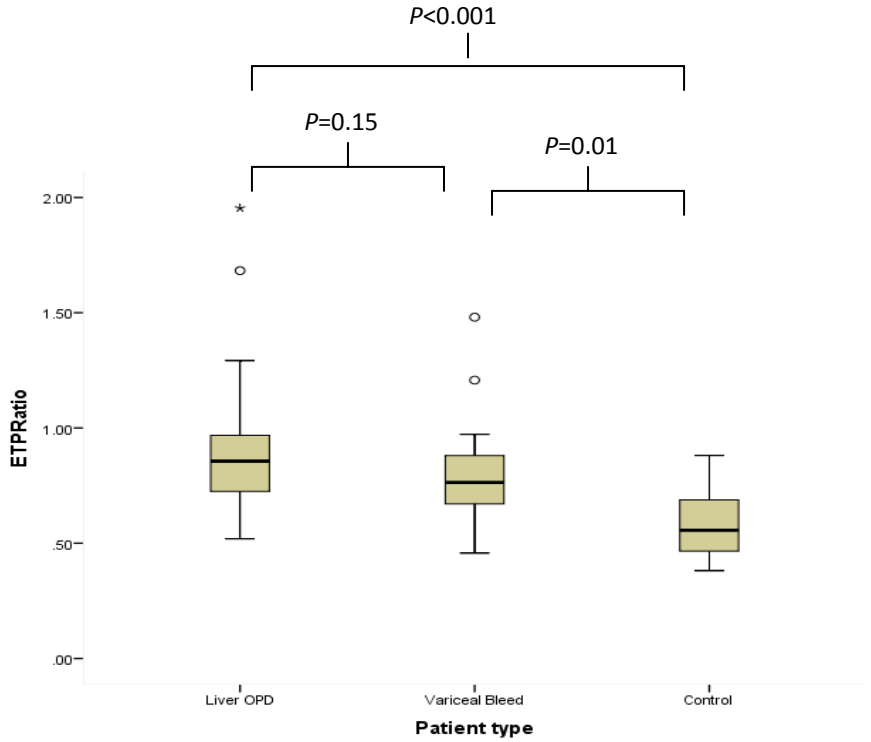
Compared to healthy controls, the ETP (the total amount of thrombin that the test plasma can generate) and the peak height of thrombin generation in cirrhotics with AVH was significantly lower than healthy controls ($p<0.01$ for both comparisons) ***(Table 8.3)***. In the presence of Protac® there was no longer a difference in the ETP between patients with AVH and controls, although the ETP ratio was significantly higher in patients with bleeding (0.8 vs. 0.6, $p=0.01$) ***(Figure 8.5)***; this reflects the relative protein C deficiency in patients with cirrhosis. Patients with AVH were able to generate thrombin faster than healthy controls as evidenced by a shorter lagtime to thrombin generation ($p=0.02$) and shorter time to peak thrombin generation ($p<0.01$) in the presence of Protac. The relative reduction in ETP after addition of Protac® in cirrhotics with AVH was 19%, in non-bleeding cirrhotics 13% and in healthy controls 43% ***(Table 8.3)***.

Table 8.3: Thrombin generation parameters in bleeding cirrhotics, non-bleeding cirrhotics and healthy controls

Parameter mean (sd)	Bleeding Cirrhotics (n=20)*		Non-Bleeding cirrhotics (n=43)		Healthy controls (n=28)	
	Without Protac	With Protac	Without Protac	With Protac	Without Protac	With Protac
Lagtime (min)	2.7 (1.2)	3.2 (1.4)	3.0 (1.9)	3.6 (3.5)	3.1 (0.4)	4.0 (0.9)
Peak (nM)	335.6 (122.2)	279.1 (128.2)	333.9 (112.2)	288.4 (86.9)	432.0 (78.1)	347.2 (57.8)
Time to peak (min)	4.8 (1.4)	5.3 (1.6)	5.4 (2.7)	5.8 (3.5)	6.1 (0.8)	7.0 (1.0)
ETP (nmol/L)	1893.9 (580.4)	1530.2 (780.5)	1843.5 (540.3)	1612.2 (533.2)	2654.3 (373.6)	1527.10 (311.8)

* $p>0.05$ for all comparisons of parameters of the curve without Protac between bleeding and non-bleeding cirrhotics.

Figure 8.5: ETP ratio bleeding cirrhotics, non-bleeding cirrhotics and healthy controls



Box plots demonstrating median and interquartile range, outliers represented by individual dots. Liver OPD=Stable, non-bleeding cirrhotics from out-patients; Variceal bleed=Cirrhotics with Acute Variceal Haemorrhage; Controls=Healthy Volunteers.

8.4.3.4 Thromboelastometry and fibrinolysis in bleeding and non-bleeding patients

There was no difference in the clotting time between cirrhotics with AVH compared to cirrhotics without bleeding (55.7 vs. 52.1, p=0.16). However, after initial clot formation, there was a significant prolongation of the CFT (159.4 vs. 116.4, p<0.05), reduction in the alpha-angle (62.5 vs. 70.9, p<0.01) and reduction in the maximum clot firmness (49.4 vs. 57.3, p≤0.01) in bleeding compared to non-bleeding patients respectively. The degree of fibrinolysis was similar but excessive in both bleeding and non-bleeding patients (ML = 14.2% vs. 12.8%, p=0.25) (Table 4). After spiking samples with the antifibrinolytic aprotinin (APTEM test), there was a significant reduction in the lysis index in both bleeding patients (14.2 vs. 7.2, p<0.01) and in non-bleeding patients (12.8 vs. 10.1, p<0.01), together with an increase in the maximum clot firmness in bleeding patients (49.4 vs. 53.7, p=0.008) ***(Table 8.4)***.

Table 8.4: ROTEM profile in bleeding and non-bleeding patients

ROTEM Parameter	Bleeding cirrhotics (n=20)	Non-Bleeding cirrhotics (n=43)
EXTEM		
CT (secs)	55.7 (9.5)	52.1 (12.2)
CFT (secs)	159.4 (73.2)*	116.4 (75.5)
Alpha-angle (degrees)	62.5 (9.8)**	70.9 (8.6)
MCF (mm)	49.4 (6.9)**	57.3 (9.9)
ML (%)	14.2 (2.8)	12.8 (5.0)
LI30	99.5 (1.0)	99.6 (1.2)
LI60	89.9 (1.7)	90.6 (3.5)
FIBTEM		
MCF (mm)	16.1 (6.6)*	12.4 (2.9)
APTEM		
ML (%)	7.2 (4.6)	10.1 (4.9)
MCF (mm)	53.7 (7.5)	55.9 (12.7)
LI30	99.6 (0.9)	99.8 (0.9)
LI60	95.3 (3.9)	93.8 (3.3)

* = $p<0.05$ for comparison of value in bleeding cirrhotics vs. non-bleeding cirrhotics.

** $p\leq0.01$ for comparison of value in bleeding cirrhotics vs. non-bleeding cirrhotics.

All values expressed as mean (sd)

8.4.3.5 Results of *ex vivo* blood component replacement on coagulation function

Ex vivo spiking with lower dose (1.2mg/ml) FgC led to a significant reduction in the CFT in comparison to the baseline values (152.9s vs. 121.9s, $p<0.05$) together with improvement in the size of the alpha-angle (60.6^0 vs. 70.8^0, $p<0.05$). Supplementation with a higher dose of fibrinogen (2.4. mg/ml) lead to an even greater reduction in the CFT (152.9s vs. 104.1s, $p<0.05$) and further improvement in the alpha-angle (60.6^0 vs. 79.7^0, $p<0.05$) ***(Table 8.5)***.

The incremental platelet count in the spiked sample was $35x10^9$ ml for the low dose (from a baseline of $70x10^9$ to $105x10^9$, i.e. equivalent to the transfusion of 1 adult therapeutic dose of platelets) and $64x10^9$ ml for the high dose (from a baseline of $70x10^9$ to $134x10^9$, i.e. equivalent to the transfusion of 2 adult therapeutic doses of platelets), which were appropriate and in keeping within UK blood transfusion parameters which estimate a $20\text{-}40x10^9$ immediate rise in platelet count after one adult therapeutic dose (http://transfusionguidelines.org.uk). *Ex vivo* spiking with low dose platelets lead to an increase in the overall maximum clot firmness (49.2 mm vs. 54.0 mm, $p=0.009$), and the higher dose (i.e. two adult doses) lead to a significant reduction in the CFT 150.7 vs. 104.9, $p=0.04$) and an even greater increase in the overall maximum clot firmness (49.2 mm vs. 59.4 mm, $p=0.002$). Neither FFP (low and high dose) nor PCC (low or high dose) had any significant impact upon any ROTEM parameters ***(Table 8.5 & Figure 8.6)***.

Table 8.5: ROTEM results following spiking of whole blood with various blood components in patients with cirrhosis and AVH†

ROTEM EXTEM Parameter	Baseline	FgC		FFP		PCC		Platelets	
		Low	High	Low	High	Low	High	Low	High
CT (secs)	53.9 (7.3)	49.9 (5.4)	55.6 (5.6)	56.7 (8.8)	58.5 (9.1)	51.3 (5.6)	54 (8.1)	57.2 (11.4)	54.4 (14.4)
CFT (secs)	150.7 (69.3)	121.9* (53.4)	104.1* (53.7)	170.7 (86.5)	182.0 (77.4)	152.7 (67.0)	159.3 (63.1)	128.0 (22.7)	104.9* (6.7)
Alpha-angle (degrees)	60.6 (12.3)	78.8* (6.4)	79.7* (6.1)	62.7 (6.9)	64.8 (4.1)	66.1 (10.9)	65.7 (11.4)	66.2 (6.1)	70.9 (6.1)
MCF (mm)	49.2 (4.6)	51.5 (5.8)	53.4 (7.0)	47.3 (3.8)	45.7 (4.1)	50.6 (5.0)	49.7 (4.9)	54.0** (2.5)	59.4** (1.0)

* = $p<0.05$ compared to baseline ROTEM value.

** $p\leq0.01$ compared to baseline ROTEM value.

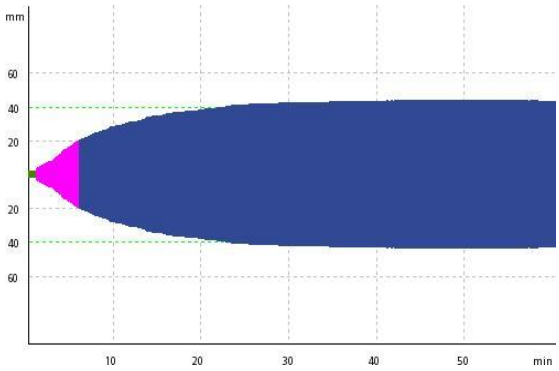
† Spiking results of 12/20 patients with acute variceal bleeding.

All values expressed as mean (sd)

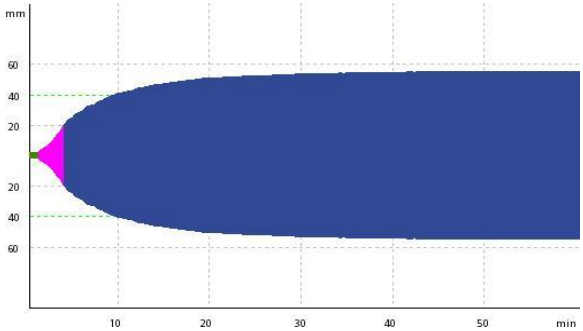
8.4.3.6 Independent laboratory predictors of overall clot strength

After adjustment for each variable in a stepwise multiple linear regression model (model adjusted for Hb, fibrinogen, platelet, albumin, urea, bilirubin as well as all individual pro- and anti-coagulant factors), the only independent predictors of overall EXTEM MCF were the platelet count (beta co-efficient 0.06, 95% CI 0.04 – 0.08, $p<0.001$) and fibrinogen level (beta co-efficient 4.26, 95% CI 2.5 – 6.1, $p<0.001$). The adjusted R^2 statistic for the model including only the platelet count was 0.623 and for the model containing both the platelet count and fibrinogen level was 0.753.

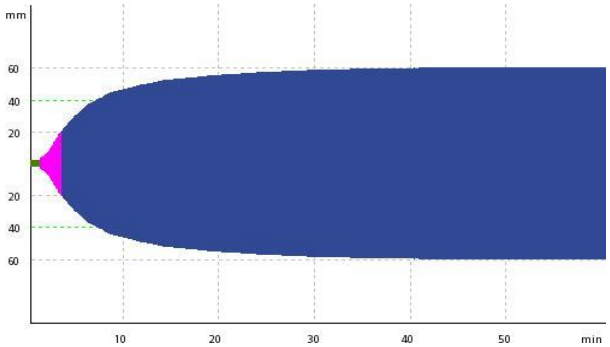
Figure 8.6: Real time ROTEM traces following acute variceal haemorrhage and *ex vivo* platelet spiking



2a: Baseline EXTEM profile in a patient with AVH



2b: EXTEM profile after spiking with equivalent of one adult therapeutic dose



2c: EXTEM profile after spiking with equivalent of two adult therapeutic doses

Figure 2: Example of EXTEM tracing in a patient with acute variceal haemorrhage. Baseline trace (2a- platelet count 107) after low dose *ex vivo* platelet spiking (2b-platelet count in spiked sample 137) and high dose *ex vivo* platelet spiking (2c-platelet count in spiked sample 166). In this example, platelet supplementation decreased the clot formation time (300s, 168s, 141s respectively), increased the alpha-angle (44^0, 58^0, 63^0 respectively) and increased the maximum clot strength (44mm, 55mm, 60mm respectively).

8.5 Discussion

This study reports on changes in the haemostatic balance in patients with cirrhosis presenting with AVH. These patients are often heavily but inconsistently transfused with blood components, coagulation factors and platelets, introducing the risks associated with both excessive transfusion (exacerbation of portal hypertension and further bleeding, lung injury, thrombosis) (Villanueva et al., 2013) or under-transfusion. The uncertainty surrounding appropriate use of coagulation factors and platelets following AVH is acknowledged by expert consensus Baveno guidelines which are unable to make recommendations on their use (de Franchis, 2010).

The results indicate that patients with AVH have a similar thrombin generation potential to a group of non-bleeding cirrhotics with similar severity of cirrhosis, despite greater prolongation of the PT. In comparison to a group of healthy controls, although the overall thrombin generation potential was reduced, patients with AVH demonstrated more rapid thrombin production, likely related to the increased availability of factor VIII. This rapid thrombin production, in addition to the relative resistance of plasma from cirrhotics with AVH to activated protein C, translated into an overall enhanced thrombotic potential as demonstrated by the ETP ratio. The preserved results of thrombin generation were confirmed by the normal clotting time on ROTEM. However, after enhanced initial clot formation, other key components of coagulation were deranged in bleeding patients on ROTEM. This included a prolonged CFT and alpha angle (reflecting fibrin polymerization and cross linkage through the interaction between fibrin and platelets), a reduced MCF (reflecting the interaction between platelets and fibrinogen) and excessive fibrinolysis. Although levels of factors II and X were lower in patients with AVH, levels of the remaining pro and anticoagulants were maintained compared to controls, with the exception of highly elevated levels of FVIII.

Levels of fibrinogen and platelet counts were reduced in patients with AVH compared to non-bleeding controls.

The net effect of this is that in patients with AVH, similar to patients with stable cirrhosis, there is sufficient pro-coagulant material to generate clot formation, not reflected by the prolonged PT suggesting hypocoagulation. These observations are consistent with the results of our *ex vivo* model. E*x vivo* supplementation with pro-coagulant factors in the form of FFP or PCC had no influence on ROTEM coagulation parameters. These results may also provide a reason for the lack of effectiveness of procoagulant FVIIa replacement to control variceal bleeding (Bosch et al., 2004; Bosch et al., 2008).

In the *ex vivo* model, supplementation with fibrinogen and platelets improved the kinetics of clot formation in a dose-dependent manner. Repletion of fibrinogen improved the rapidity of clot propagation (CFT and alpha angle), and platelet transfusion improved overall clot strength. Fibrinogen is a major procoagulant substrate of thrombin, and formation of fibrin is a critical component of coagulation (Lang et al., 2009). There is evidence from dilutional models of thrombocytopenia in healthy volunteers that supplementation with fibrinogen improves coagulation parameters on thromboelastography even in patients with a platelet count of $<20x10^9$/L (Lang et al., 2009). In thrombocytopenic patients with AVH, fibrinogen supplementation may have resulted in the improved coagulation profile by virtue of larger quantities of fibrinogen being captured by platelets via their abundant GPIIb/IIIa receptors (40,000-50,000 copies per platelet) (Wagner et al., 1996). Although FFP also contains low levels of fibrinogen, this may have been insufficient to influence the kinetics of clot formation. A previous study of critically ill patients with cirrhosis admitted to intensive care units

reported that platelet transfusion was the only component to significantly improve thromboelastography parameters (Clayton et al., 1995). These findings, in conjunction with the results of the multivariable linear regression model, which suggested that the platelet count and fibrinogen concentration were important independent determinants of overall clot strength, highlight the need for interventional studies to assess the clinical importance of the use of platelet transfusions and fibrinogen supplementation following AVH in patients with cirrhosis.

Whilst it is accepted that there is a relatively high prevalence of hyperfibrinolysis in patients with stable liver cirrhosis (Ferro et al., 2009; Rijken et al., 2012), no studies have documented this in patients with AVH. We found that the magnitude of fibrinolysis (lysis index) was similar in patients with AVH and stable liver disease. After spiking blood samples with aprotinin, and inhibitor of plasmin, the correction of fibrinolysis was much greater in patients with AVH and thereby resulted in an additional improvement in clot strength. Hyperfibrinolysis may act not only as an additional precipitant to variceal bleeding, but may also delay primary haemostasis thereby aggravating severity of bleeding and potentially promote further bleeding (Ferro et al., 2009). A large RCT in the UK is underway to assess whether early administration of an antifibrinolytic is able to reduce mortality, further bleeding and transfusion requirements in patients with acute gastrointestinal bleeding, including those with cirrhosis and variceal bleeding (ISRCTN11225767).

The strengths of this study include obtaining blood samples at first presentation with AVH, thereby representing a true picture of coagulation prior to transfusion of any components which may have confounded the results. The methodology used for thrombin generation and the Protac modified assay was based upon validated

methodology in patients with stable liver disease (Gatt et al., 2007; Gatt et al., 2010). The spiking protocol has been validated in a recently published series of patients with traumatic bleeding (Rourke et al., 2012). Non-bleeding were well matched for age, disease severity and aetiology and therefore an appropriate comparator group. The limitation of thromboelastometry is that it is conducted under low shear conditions which may not fully represent *in vivo* conditions. The effect of blood components replacement was *ex vivo* which can only suggest what the clinical effects of replacement may be.

Thromboelastometry is a bed-side test which detects functional alterations of platelets and coagulation proteins as well as the interaction between cellular elements and plasma factors. It is increasingly used in cardiac surgery, the management of acute traumatic haemorrhage and in liver transplant surgery (Blasi et al., 2012) where it facilitates rapid, goal-directed transfusion support. A recently published Health Technology Assessment recommended the use of thromboelastometry routinely in liver transplant surgery based on evidence that it reduces inappropriate transfusion, is cost-effective and has a positive impact on patient outcomes including deaths, complication and infections (Craig J, 2008). To date it has not been used to any great extent in hospitalised patients with liver disease and the potential benefit (and cost-effectiveness) of wider use in patients with variceal bleeding requires further research.

8.6 Summary

Coagulation derangements following AVH are complex and not reflected by static indices such as PT. Patients with cirrhosis and AVH have preserved thrombin generation and sufficient pro-coagulant material to support clot formation raising uncertainty of the benefit or need for transfusion of pro-coagulant factors such as plasma. However, following clot formation, kinetics and clot strength were poor and our results indicate that there may be a benefit from early administration of fibrinogen, platelet transfusion and antifibrinolytics. These results provide important data for the design and conduct of RCTs of transfusion strategies in patients with liver cirrhosis and AVH.

9 Chapter Nine

Red Blood Cell transfusion practice in patients with acute upper gastrointestinal bleeding

9.1 Introduction

Current guidelines for RBC transfusion triggers in AUGIB are largely based on expert opinion. BSG guidelines recommend RBC transfusion when the Hb is <10 g/dL (Palmer, 2002) but a more recent international expert consensus guideline on the management of patients with non-variceal AUGIB advocates transfusion when Hb is <7g/dL (Barkun, 2010). Practice may be expected to vary widely, as has been demonstrated in observational studies and surveys of transfusion practice in critical care and cardiac surgery (Bennett-Guerrero et al., 2010; Hebert et al., 1998). Since there are no such data in AUGIB and, as a consequence of recent concerns that transfusion may have an adverse outcome, this survey was designed to characterise attitudes towards transfusion practice in patients presenting with AUGIB.

9.2 Aims

The aim of this study was to survey a broad range of UK clinicians about their RBC transfusion practice in AUGIB using case based scenarios (***Table 9.1)***. Specific aims included determining:

1) Whether there was a difference in the Hb trigger for transfusion between scenarios.

2) Whether there was a difference in the Hb trigger for transfusion between physicians and surgeons, and grade of clinician seniority.

3) Whether the Hb trigger for transfusion was affected following a range of possible endoscopic diagnoses.

9.3 Methods

The study methodology was described in Chapter 2.2.

9.3.1 Statistical methods:

Because the outcome was ordinal, proportional odds models were used to test whether there was a difference in the Hb triggers for RBC transfusion. Results from a proportional odds model are expressed as odds ratios (OR), which represent the odds of choosing a higher Hb trigger for transfusion. For example, if the OR between clinical scenario 2 compared to clinical scenario 1 was 1.5, this would indicate that clinicians were 50% more likely to choose a higher Hb trigger for scenario 2 than for scenario 1.

Table 9.1 Outline of the six clinical scenarios in the survey

Scenario 1 (Rockall Score 0)

A 40 year old man with no known co-morbidities presents with a 1 day history of melaena. He is otherwise entirely asymptomatic. Admission observations document a blood pressure (BP) of 125/78, heart rate (HR) 76 beats per minute (bpm). Other than melaena on PR (per rectal examination), clinical examination is unremarkable, with no evidence of a volume deficit. At what haemoglobin concentration (Hb, g/dL) would you prescribe a red cell transfusion for this patient?

Scenario 2: (Rockall Score 2)

A 28 year old man presents with 500mls of fresh haematemesis, preceded by a 12 hour history of vomiting after an alcohol binge. He has no past medical history and is a keen athlete. On arrival he has a BP of 90/60, HR of 120 bpm. The patient is now haemodynamically stable following successful resuscitation with crystalloid and no longer has evidence of a volume deficit. Examination is otherwise unremarkable. At what Hb (g/dL) would you prescribe a red cell transfusion for this patient?

Scenario 3: (Rockall Score 1)

A 65 year old male presents with 3 episodes of melaena in the proceeding 24 hours. He is a life-long smoker and is overweight although has no significant co-morbidities. He takes 75mg of aspirin daily of his own accord. Admission observations document BP of 120/75, HR of 90 bpm. Other than melaena on PR, clinical examination is unremarkable, with no evidence of a volume deficit. At what Hb (g/dL) would you prescribe a red cell transfusion for this patient?

Scenario 4: (Rockall Score 4)

An 80 year old woman presents with a 2 day history of melaena. She has a past history of a myocardial infarction 2 years previously and a coronary artery stent. She is taking both aspirin and clopidogrel. Her admission observations document a BP-102/78, HR- 88 bpm (she is not on beta-blockers). She has melaena on PR, but examination is otherwise unremarkable. She has no evidence of a volume deficit. At what Hb (g/dL) would you prescribe a red cell transfusion for this patient?

Scenario 5: (Rockall Score 7)

An 81 year old man presents with melaena. He has a past history of mild chronic renal impairment, cerebrovascular disease and congestive cardiac failure. He takes regular aspirin and dipyridamole. On admission his BP is 99/69 and HR 105 bpm. He has no clinical signs of heart failure and his BP and tachycardia improve following cautious crystalloid infusion (BP-115/80, HR-88).His baseline Hb is within the normal, gender matched range. At what Hb (g/dL) would you prescribe a red cell transfusion for this patient?

Scenario 6: (Rockall Score 5)

A 50 year woman presents with melaena following a 24 hour binge of alcohol. She has known alcoholic liver disease, with portal hypertension and varices. On admission her BP is 90/60 and HR-105 bpm. She is now haemodynamically stable following fluid resuscitation (BP-110/70, HR-85 BPM) with no evidence of a volume deficit. At what Hb (g/dL) would you prescribe a red cell transfusion for this patient?

9.4 Results

Of 830 respondents ***(Table 9.2)***, 10 were incomplete and another 5 were below the grade of speciality trainee, so were excluded. For the BSG, 34/290 email invitations were undeliverable; 144/256 (58%) responded. For TIG, 31/287 email invitations were undeliverable and 128/256 (54%) responded. For SAM the response rate was 346/740 (46%) and for AUGIS 197/457 (43%), giving an overall response rate of 48% (815/1709). 98% respondents directly cared for patients presenting with AUGIB and 96% made decisions about RBC transfusions. 70% reported familiarity with national guidelines of AUGIB.

Table 9.2: Characteristics of respondents

Characteristics	Respondents n=815 % (n)
Primary Specialty	
Consultant Physician*	7 (55)
Consultant- Acute Medicine	14 (116)
Consultant Gastroenterologist **	18 (144)
Consultant Surgeon	16 (132)
Specialist trainee- Acute Medicine†	17 (140)
Specialist trainee- Gastroenterology	16 (128)
Specialist trainee- Medicine‡	5 (46)
Specialist Trainee- Surgery	7 (54)
Gender	
Male	76 (616)
Year of Graduation	
After 2004	3 (25)
1995-2004	48 (390)
1985-1994	36 (291)
1975-1984	10 (83)
Before 1975	3 (26)
Type of Practice	
District general hospital <500 beds	17 (135)
District general hospital >500 beds	39 (317)
District general hospital 500-1000 beds	2 (19)
University teaching hospital	42 (344)

* without a special interest in Gastroenterology

** whether or not an acute-take physician as well

† Specialist trainee refers to the grade of specialist registrar or specialist trainee 3+ or above

‡ Primary specialty other than gastroenterology and involved in acute medicine

9.4.1 Differences in transfusion trigger according to patient characteristics:

The Hb transfusion trigger differed significantly between the 6 scenarios ($p<0.001$) ***(Table 9.3 and Figure 9.1).*** The modal Hb transfusion trigger in scenario one (young man with no co-morbidities), scenario two (young man with features of shock) and scenario three (65 year old male smoker who could have occult ischaemic heart disease) was 7.1-8 g/dL (41%, 36.6% and 37.3% of respondents respectively). For scenarios four and five, both representing older patients with ischaemic heart disease, the modal Hb transfusion trigger was in the range of 9.1-10 g/dL (41.5% and 35.3% respectively). A Hb trigger of 8.1-9g/dL was the most frequently selected trigger (35.1%) in scenario six, representing a patient with alcoholic liver disease and likely variceal haemorrhage.

A Hb trigger of >9g/dL was chosen by only 6.4% and 13.3% of respondents for scenarios 1 and 2, compared to 45.2% and 38.3% for scenarios 4 and 5, respectively. In response to the scenario of variceal bleeding, 32.6% of respondents selected a trigger of >9 g/dL. Very few clinicians reported that they would transfuse at a Hb trigger >10g/dL in all scenarios (0.4%, 2%, 1.7%, 3.7%, 3%, 3.2% for scenarios 1-6 respectively).

Figure 9.1: Transfusion triggers for the six clinical scenarios

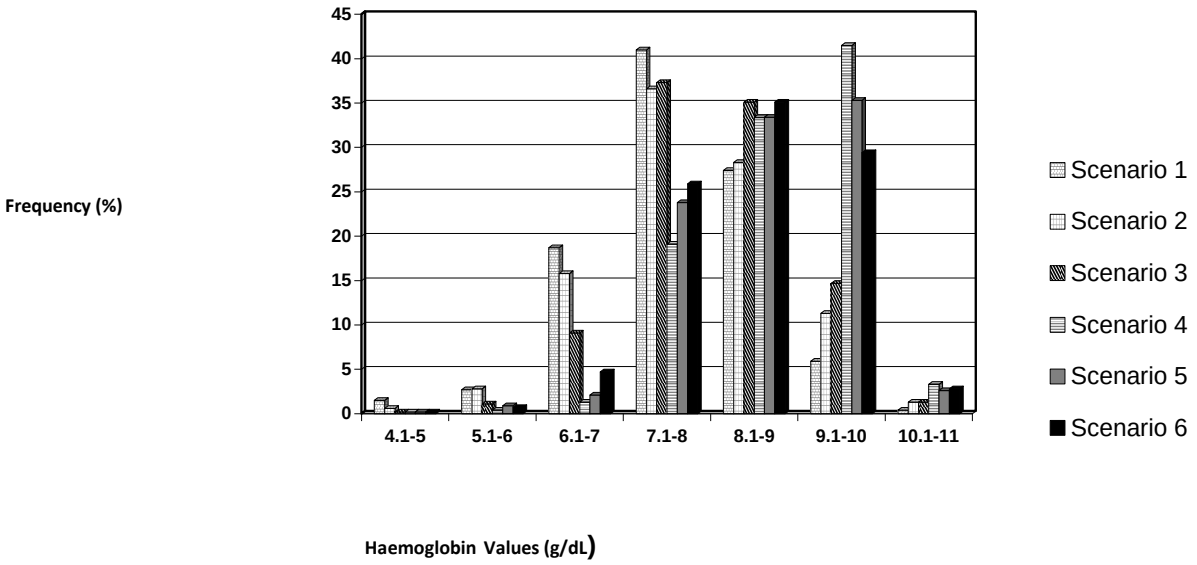


Table 9.3: Difference in Haemoglobin trigger for each main scenario

Scenario	OR*	95% CI	p-value
1	1.0	-	-
2	1.45	1.30 to 1.62	<0.001
3	2.22	2.00 to 2.45	<0.001
4	8.04	6.97 to 9.27	<0.001
5	6.00	5.18 to 6.96	<0.001
6	4.70	4.06 to 5.44	<0.001

*Reference category scenario 1 OR=1.0

The OR represents the odds of a clinician choosing a higher Hb transfusion trigger compared to scenario 1. For example, the OR for scenario 2 is 1.45. This indicates that clinicians are 45% more likely to choose a higher Hb threshold to transfuse at for scenario 2 than for scenario 1

9.4.2 Differences in transfusion trigger according to endoscopic characteristics

The three theoretical endoscopic diagnoses all resulted in a higher Hb trigger compared to the baseline scenario ($p<0.01$; ***Table 9.4***). This was most pronounced for an actively bleeding duodenal ulcer treated successfully at endoscopy (OR 2.54, 95% CI 2.26-2.85 for scenario 1; OR 1.47, 95% CI 1.35-1.59 for scenario 4).

9.4.3 Differences in transfusion trigger according to clinician characteristics:

There was significant variation in the mean Hb transfusion trigger between clinical specialty groups for all clinical vignettes, other than for scenario 5 ***(Table 9.5)***. Surgeons chose lower Hb triggers for transfusion than physicians across all 6 scenarios ($p<0.005$) ***(Table 9.6)***. Clinicians who had graduated more recently were also more likely to transfuse at a lower Hb trigger compared to clinicians who had graduated less recently, other than for scenario 4 (acute variceal bleeding) ***(Table 9.7)***. Examples of free comments are highlighted in ***Table 9.8***.

Table 9.4: Difference in haemoglobin trigger in relation to endoscopic diagnosis

Scenario	OR*	95% CI	p-value
Scenario 1			
Duodenal ulcer with clean base	1.10	1.03 to 1.18	0.005
Mallory Weiss tear with clot but no active bleeding	1.13	1.04 to 1.22	0.003
Duodenal ulcer with active bleeding from central vessel treated successfully at endoscopy	2.54	2.26 to 2.85	<0.001
Scenario 4			
Duodenal ulcer with clean base	0.94	0.90 to 0.99	0.012
Mallory Weiss tear with clot but no active bleeding	0.96	0.90 to 1.01	0.12
Duodenal ulcer with active bleeding from central vessel treated successfully at endoscopy	1.47	1.35 to 1.59	<0.001

*Reference category baseline scenario OR =1.0
The OR represents the odds of choosing a higher Hb transfusion trigger compared to the baseline scenario.

Table 9.5: Difference in haemoglobin trigger- Surgeons versus Physicians

Scenario	OR*†	95% CI	p-value
1	0.46	0.33 to 0.63	<0.001
2	0.35	0.26 to 0.49	<0.001
3	0.48	0.35 to 0.66	<0.001
4	0.61	0.45 to 0.84	0.002
5	0.63	0.46 to 0.86	0.004
6	0.59	0.44 to 0.81	0.001

*Reference category physician OR =1.0. The OR represents the odds of choosing a higher Hb transfusion trigger compared to scenario 1.
†Odds ratio adjusted for year of graduation

Table 9.6: Mean (SD) haemoglobin transfusion threshold per scenario according to primary specialty

Primary specialty	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Consultant Physician (n=55)	8.0 (1.0)	8.3 (1.0)	8.5 (0.9)	9.1 (1.0)	9.0 (1.0)	8.9 (1.0)
Consultant Acute Medicine (n=116)	7.9 (1.0)	8.2 (1.0)	8.3 (0.9)	8.8 (0.8)	8.6 (0.9)	8.8 (1.0)
Consultant Gastroenterologist (n=144)	7.7 (1.0)	8.0 (1.1)	8.3 (1.0)	8.9 (1.0)	8.6 (1.0)	8.5 (1.0)
Consultant Surgeon (n=132)	7.5 (0.9)	7.7 (1.0)	8.0 (0.8)	8.8 (0.8)	8.6 (0.9)	8.4 (0.8)
Trainee Acute Medicine (n=140)	7.7 (0.9)	7.9 (1.0)	8.0 (0.9)	8.9 (0.8)	8.8 (0.9)	8.7 (0.9)
Trainee Gastroenterology (n=128)	7.6 (0.9)	7.9 (1.2)	8.1 (0.9)	8.7 (0.9)	8.6 (0.9)	8.2 (1.0)
Trainee Medicine (n=46)	7.7 (0.6)	7.6 (0.6)	7.7 (0.6)	8.7 (0.6)	8.6 (0.7)	8.5 (0.6)
Trainee Surgery (n=54)	7.3 (1.0)	7.4 (1.2)	8.0 (1.2)	8.5 (0.9)	8.4 (0.9)	8.3 (0.9)
Overall (n=815)	7.7 (1.0)	7.9 (1.1)	8.1 (0.9)	8.8 (0.9)	8.7 (0.9)	8.5 (1.0)

*Mean and SD were calculated using an interval regression model which accounts for the fact the data are in intervals

9.4.4 Differences in transfusion trigger according to clinician characteristics:

There was significant variation in the mean Hb transfusion trigger between clinical specialty groups for all clinical vignettes, other than for scenario 5 ***(Table 9.5)***. Surgeons chose lower Hb triggers for transfusion than physicians across all 6 scenarios ($p<0.005$) ***(Table 9.6)***. Clinicians who had graduated more recently were also more likely to transfuse at a lower haemoglobin trigger compared to clinicians who had graduated less recently, other than for scenario 4 (acute variceal bleeding) ***(Table 9.7)***. Examples of free comments are highlighted in ***Table 9.8***.

Table 9.7: Difference in haemoglobin trigger according to clinician year of graduation

Scenario	Year	OR*	95% CI	p (overall)
1	> ‘04	0.56	0.27 to 1.13	0.04
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.39	0.97 to 1.99	
	’75 – ‘84	1.99	1.17 to 3.40	
	< ‘75	1.44	0.66 to 3.14	
2	> ‘04	0.89	0.42 to 1.88	0.002
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.61	1.12 to 2.32	
	’75 – ‘84	3.05	1.79 to 5.21	
	< ‘75	1.81	0.84 to 3.87	
3	> ‘04	0.54	0.26 to 1.15	0.006
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.64	1.14 to 2.36	
	’75 – ‘84	2.35	1.38 to 4.00	
	< ‘75	1.76	0.79 to 3.93	
4	> ‘04	1.05	0.47 to 2.34	0.32
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.42	0.98 to 2.05	
	’75 – ‘84	1.51	0.89 to 2.57	
	< ‘75	1.87	0.82 to 4.27	
5	> ‘04	1.46	0.68 to 3.11	0.08
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.57	1.09 to 2.26	
	’75 – ‘84	1.81	1.06 to 3.09	
	< ‘75	1.13	0.51 to 2.53	
6	> ‘04	0.52	0.24 to 1.12	0.07
	’95 – ‘04	1.00	-	
	’85 – ‘94	1.53	1.07 to 2.19	
	’75 – ‘84	1.44	0.86 to 2.43	
	< ‘75	1.36	0.62 to 3.01	

*Reference category- graduation between years 1995 to 2004, OR=1.0. Odds ratios adjusted for year of graduation and whether the respondent was a consultant.

Table 9.8: Examples of free text comments to each scenario

Scenario 1	Scenario 2
"I would only prescribe red cells for Hb less than 8 ; otherwise iv iron"	"I guess it would depend on how unwell he looks. I would not necessarily prescribe blood on the basis of a Hb number"
"Would be concerned that following some fluid/time that Hb will drop further with dilution"	"Potential antibody reaction at his early age could make future blood transfusions more complicated"
"Below eight is our hospital policy"	"High risk - very compromised haemodynamically for fit man"
"We have a hospital protocol to transfuse if Hb less than 10 in UGIB"	"Below 6 - definitely, 7-8 maybe - after discussion with the patient"
"He is haemodynamically stable so may not need transfusing at all if can be rapidly OGD'ed" (abbreviation for Gastroscopy).	"The juniors always err on the side of over-transfusion"
"Would expect to be heavily criticised for not transfusing at 8.1 by colleagues"	

Scenario 3	Scenario 4
"I would be concerned that he may have occult ischemic heart disease"	"We would endoscope the patient quickly and know the diagnosis before deciding about transfusion"
"Any signs of IHD on ECG would push the trigger up"	"If she had signs or symptoms of myocardial ischemia at a higher Hb, i.e. 10g/dl I would prescribe red cell transfusion to enhance the oxygen carrying capacity. Normally, however, I seldom transfuse unless the Hb falls below 8g/dl."
"Transfuse blood only if symptomatic or fails to rise with iron"	"I would give transfusion at a higher Hb level if she had symptoms of angina or evidence of ischemia on ECG."

Scenario 5	Scenario 6
"Would transfuse slowly probably with CV (central venous) pressure monitoring"	"I would not want to overtransfuse"
"With very cautious volume delivery in view of comorbidity"	"This patient needs an urgent endoscopy before you make any decision"
"As haemodynamically stable now, <7 is the cut-off for transfusion"	"Transfuse to an HB of no more than 8"
"With his haemo-dilution, he is at risk of developing complications, given his co-morbidities, hence low trigger for transfusion"	"Assuming haemostasis achieved - in suspected variceal bleeds or massive GI bleeds I will often use blood as resuscitation fluid, guided by blood pressure & pulse, rather than wait to see a recorded low Hb"

9.5 Discussion

This survey highlights widespread variation in attitudes to RBC transfusion in patients presenting with AUGIB in the UK. It also highlights differences between belief and practice, with belief that, in some circumstances, restrictive use of RBCs is appropriate, but discordant with some of the observed practice from the UK national audit; for example, in this survey, <4% of clinicians declared that they would ever transfuse a patient with a presenting Hb >10 g/dL, whereas in the large UK national audit 15% of all early RBC transfusions (within 12 hours of presentation to hospital) were administered to patients with a presenting Hb >10g/dL, of whom 38% had no features of haemodynamic compromise whatsoever (Hearnshaw et al., 2010). Similarly, 50% of all patients who were haemodynamically stable with a Hb between 8.1-10 g/dL were transfused in the national audit. There are, of course, limitations in making direct comparisons given that the large national audit was a comprehensive picture of "real-life" processes of care and outcomes following presentation with AUGIB to a large number of UK hospitals, capturing a far wider range of disease acuities than can be comprehensively represented in the format of a case-based survey; however, opinions in this survey were gauged from the very same healthcare system, institutions and clinicians whom took part in the national audit.

Shock did not appear to lower the theoretical threshold for transfusion. The only clinically relevant difference between scenarios 1 and 2 was the presence of haemodynamic instability in the latter (which responded to crystalloid), but Hb triggers for transfusion were similar. This suggests that the absence of co-morbidity may have dictated the decision to restrict transfusion. This is consistent with the response to scenario 3, where there were only risk factors, but no documented ischaemic heart disease. The presence of ischaemic heart disease in scenarios 4 and 5 was associated

with a 6 to 8-fold increase in the likelihood of selecting a higher Hb trigger for transfusion (OR 8.04, 95% CI 6.97-9.27 for scenario 4 compared to scenario 1), presumably in the belief that this would facilitate oxygen delivery. Whilst only an RCT will answer the question of whether differing blood transfusion strategies affect morbidity and mortality in patients with coronary artery disease, existing evidence suggests that a transfusion trigger of <8 g/dL has no negative impact in this group of patients.

Clinical diagnosis had a variable impact on transfusion threshold. In scenario 6 (acute variceal bleeding), the modal Hb trigger for transfusion was 8.1-9 g/dL, with a third (32.6%) selecting a trigger >9g/dL. Gastroenterologists have long advocated restrictive transfusion in patients with variceal bleeding, to avoid adversely raising portal pressures and precipitating further bleeding. Indeed, in patients with AUGIB secondary to portal hypertension there is evidence that RBC transfusion to levels of > 8g/dL has an adverse effect to the extent that international consensus guidelines strongly recommend maintaining the Hb around 8g/dL, but no greater (de Franchis, 2010). Adherence to this guideline was not reflected in the current study.

Information about the endoscopic diagnosis raised the Hb transfusion trigger. This probably reflects the practice of clinicians “topping-up” patients as a precaution against re-bleeding. Training also had an impact. Surgeons were more likely to transfuse at lower Hb triggers across all of the proposed clinical scenarios; this may be a reflection of educational interventions and RCTs demonstrating safer use of restrictive transfusion triggers in a variety of surgical patients with similar, much needed, interventions lacking in medical patients. The differences found in relation to year of graduation may reflect guidelines in effect during these periods of time. The observation that only 70%

of clinicians reported familiarity with national guidelines for AUGIB is surprising warrants further investigation.

A number of themes emerged from the many free text comments. The respondents to this survey were more senior clinicians and there were several comments alluding to their perceived practice of "overtransfusion" by more junior doctors. Some clinicians felt that they would be criticised by colleagues if they prescribed restrictively. Many clinicians commented on their use of intravenous iron as a blood avoidance therapy, especially in patients who were haemodynamically stable, with a low Hb, or had stopped bleeding. Finally, several respondents quoted and expressed adherence to their own hospital guidelines for AUGIB, which further demonstrated variation in the recommended Hb triggers for transfusion ranging from 7-10 g/dL.

This study has several limitations. Firstly, the ideal method of assessing a clinician's transfusion practice is to observe daily practice, not by use of a survey of opinions which may generate idealised responses. However, survey based clinical vignettes have been shown to be a valid surrogate for chart abstraction and standardised patients (Peabody et al., 2004). Also scenario based surveys of transfusion practice in other clinical areas has been found to be reasonably consistent with actual practice patterns Secondly, the overall response rate introduces the possibility of non-response bias. However, the mean response rate for published surveys of physicians in the literature is in the order of 54% (Asch et al., 1997). Both the pilot survey and this main survey had an overall response rate in keeping with this. However, as the purpose of this survey was to assess variation in clinical opinion, it is implausible that a higher response would materially reduce the level of variation we have found. Thirdly, the case vignettes do not represent all possible AUGIB scenarios; several steps were taken to ensure accurate

content validity of our vignettes through consultation with opinion leaders in AUGIB and transfusion medicine and through pilot testing of scenarios for comprehensibility.

9.6 Summary

This study highlights widespread variation in attitudes towards RBC transfusion practice for AUGIB. Both patient and clinician characteristics influence RBC transfusion decisions. This variation provides an opportunity to optimise and improve the evidence base for transfusion in this setting. In other large clinical user groups of RBCs such as cardiac surgery, significant reductions in blood use have been observed through blood conservation programmes. Further reductions may be seen following the publication of a recent RCT demonstrating a restrictive transfusion policy was not inferior to a liberal policy after cardiac surgery (Hajjar et al., 2010). Similar initiatives, as opposed to further expert guidelines, are much needed for AUGIB which may help to rationalise transfusion practice in the leading single indication for RBCs in the UK.

10 Chapter Ten

Summary and implication of these findings

This thesis aimed to investigate how outcomes following AUGIB in the UK can be improved. Five broad themes were tackled, with a focus upon the potential for improved control of haemorrhage. This work has provided new data to inform current practice, has highlighted areas of sub-optimal and variation in care and generated data to inform research questions for the design of interventional trials in AUGIB. The main findings and implications are summarised below.

10.1 Service provision and timing of endoscopy

Compared to weekday presentations, patients presenting at weekends were more critically ill with greater delays to endoscopy (Chapter 3). There were unacceptable delays in the management of patients presenting at weekends, in particular only 38% received endoscopy within 24 hours of presentation, which falls well below the standards of care recommended by guidelines. Despite this, there was no evidence of a "weekend effect" for mortality or further bleeding. This suggests that those most likely to benefit from early endoscopy at weekends do actually receive one, which may be related to goodwill of endoscopists in hospitals without formal out of hours endoscopy rotas. It may also reflect deficiencies in weekday management. Any reduction in service provision from current levels may lead to poorer outcomes for weekend presentations.

This is the largest study to date to have investigated the association between time to endoscopy and clinical outcome following AUGIB and should help to update consensus guidelines (Chapter 4). Earlier endoscopy (<12 hours) was not associated with a reduction in mortality or need for surgery compared to later endoscopy (>24 hours).

However, in patients requiring endotherapy, endoscopy within 12 hours (versus >24 hours) was associated with a 13% reduction in the risk of further bleeding, indicating improved control of haemorrhage through the provision of more timely endoscopy in high risk patients. In addition, endoscopy after 24 hours resulted in an increase in risk adjusted length of stay of 1.7 days compared to endoscopy before 12 hours. Given that most UK hospitals admit at least one patient with AUGIB the potential cost savings to NHS trusts are substantial.

These results support the routine use of early endoscopy unless contraindications exist. Re-organisation of endoscopy services may not only increase efficiency of care but could also improve outcome in high risk patients. These data can be used both by clinicians and managers to justify the provision of formalised out of hours endoscopy rotas in those hospitals without them, and to justify job expansion for the provision of routine endoscopy at weekends as the NHS aspires to a seven day working week.

10.2 Use of radiological embolisation and surgery for refractory bleeding

This is the largest study to have reported on the use of surgery and TAE for the management of refractory bleeding (Chapter 5). Salvage surgery and/or TAE was used in <4% of cases in the modern day management of NVUGIB in the UK. Given the rates of surgery were up to 20% two decades ago, this is likely to reflect improvements in endoscopic therapy, proton pump inhibition and supportive care.

Whilst surgery remains the gold standard for the management of NVUGIB refractory to endoscopic intervention, post-operative mortality was strikingly high (29%). This is undoubtedly a reflection of the influence of co-morbidity and age in critically ill

patients with severe bleeding, although it raises questions as to the appropriateness of case selection. The study lends support to the success of TAE as a minimally invasive alternative to surgery, given that in only 9% was there failure to control bleeding after TAE and 91% undergoing TAE survived. There are obvious benefits to the use of TAE as an alternative to surgery, namely the avoidance of general anaesthesia and laparotomy in elderly patients. It remains unclear if TAE should be used as a routine alternative to surgery, or a bridge to surgery or even prophylactically in high risk lesions. Head to head trials to answer this would be challenging to conduct. It is likely that in those hospitals with access to round the clock interventional radiology there would be a natural enthusiasm for TAE prior to surgery and a future audit with similar methodology would be required to ascertain its more widespread use.

10.3 The impact of deranged coagulation on outcome in patients with NVUGIB

Similar to other clinical scenarios of major bleeding such as trauma and cardiac surgery, coagulopathy was prevalent in 16% of patients shortly after presentation with NVUGIB. Patients with coagulopathy were more critically ill, presented with more severe haemorrhage and had a five-fold increased risk of death after adjustment for confounders. Only one-third of patients with coagulopathy received plasma transfusion, suggesting uncertainty as to the benefits of correction of coagulopathy. Patients with coagulopathy should be identified early and targeted for more intensive monitoring and support. Further work is needed to understand mechanisms leading to coagulopathy, whether it is on the causal pathway to adverse outcome and whether early interventions to correct coagulopathy, as is now routine practice following trauma, could improve outcome in patients with NVUGIB.

10.4 Characteristics, management and outcomes of patients with liver cirrhosis and variceal haemorrhage and evaluation of haemostatic abnormalities and response to treatment

The incidence and prevalence of cirrhosis in the UK is rising, explaining the increase in the proportion of patients presenting with AVH. In this large cohort of patients, it was encouraging to observe reductions in mortality following AVH, although rates of further bleeding remain strikingly high (26%). This may be partly explained by the notable deficiencies in quality of care provided to patients with AVH, including inadequate use of vasopressors, antibiotics and endoscopic therapy (Chapter 7). This is a key endpoint upon which improvements in outcome should target, given that mortality is five-fold greater in those who experience further bleeding.

This study provides detailed description of the use of blood components in patients with AVH. The majority of patients received RBCs (75%) with some evidence of liberal transfusion practice, which is especially pertinent given recent RCT evidence to suggest this may be harmful (Villanueva et al., 2013). In addition, there was notable variation in the use of FFP and platelet transfusion probably reflecting uncertainty about optimal practice. Given the complex derangements in haemostasis in cirrhosis, targeted use of pro-haemostatic agents may serve to help control bleeding and prevent further bleeding.

The laboratory study is the first of its kind to characterise global changes in haemostasis in patients with AVH at the time of presentation with haemorrhage, prior to transfusion of any blood components. Despite a prolonged PT and APTT, patients with AVH had normal thrombin generation potential, due to preserved levels of individual coagulation factor levels and highly elevated factor VIII. However, quality of coagulation was poor with reduced kinetics of clot formation, reduced clot strength and excessive fibrinolysis.

In order to better understand which blood components could improve the haemostasis, whole blood from patients with AVH was spiked *ex vivo* with a variety of pro-haemostatic blood components. Coagulation factor replacement (FFP and PCC) had no influence on haemostatic potential. Administration of platelets, fibrinogen and antifibrinolytics improved the kinetics of clot formation and overall clot strength. These results question the benefit of coagulation factor transfusion after AVH and provide rationale for new trials of pro-haemostatic interventions to control bleeding and prevent further bleeding in patients with AVH.

10.5 Use of RBC transfusion for AUGIB

The cross-sectional survey of a broad range of clinicians involved in the management of patients with AUGIB confirmed variation in attitudes towards RBC transfusion, influenced both by patient and clinician characteristics (Chapter 9). Many clinicians reported that they would transfuse restrictively, which is discordant with observed practice from the national audit. Senior clinicians commented on the practice of "over-transfusion" by more junior colleagues whilst some clinicians felt they would be criticised by their colleagues for following a restrictive transfusion policy. These variations in attitudes and actual observed clinical practice from the national audit provide an opportunity to improve the evidence base for the leading single indication for RBCs in the UK through the design and conduct of RCTs and blood conservation programmes, as have been conducted in other large user groups of RBCs such critical care and surgical specialties.

10.6 Further work arsing from this thesis and related programme of work

10.6.1 The "TRIGGER" trial

Building upon the work outlined in Chapters 1.4.2 and 9 since October 2009, with the support of senior trialists, clinicians, methodologists and statisticians, I co-ordinated the "TRIGGER" trial ("Transfusion in Gastrointestinal Bleeding"; ISRCTN 85757829) in the capacity of joint Chief-Investigator. This involved designing a cluster-randomised study, obtaining peer reviewed competitive funding (NHSBT R&D; £0.18m), site selection, developing the protocol and case report forms, obtaining ethical and regulatory approvals, trial set up and training and chairing the Trial Management Group. The trial was successful and is now closed to recruitment, having enrolled 936 patients over a six month period in six UK hospitals. At the time of writing (March 2013), the statistical analysis plan has been finalised and with an aim to publish the study findings towards the end of 2013. The rationale and protocol for the trial has been published and further details are available on the dedicated trial website (www.nhsbt.nhs.uk/trigger/). The following section briefly summarises the trial rationale and methodology.

10.6.1.1 Aim

To evaluate the feasibility and safety of implementing a restrictive versus liberal RBC transfusion policy in adult patients admitted with AUGIB, in order to inform the design of a phase III trial.

10.6.1.2 Design and setting

Pragmatic, cluster randomised feasibility trial comparing two different RBC transfusion strategies in patients admitted with AUGIB. Each participating centre was randomly allocated to one of two transfusion policies, and all eligible patients in a centre were treated according to the allocated transfusion policy. The trial recruited in six UK centres. Feasibility, clinical and health economic outcome measures were collected.

10.6.1.3 Randomisation of clusters

Centres were randomised using permuted blocks without stratification or matching. Consent was sought from relevant clinical stakeholders at each centre to enable each hospital to be randomised to a transfusion policy. Individual eligible participants were approached for use of routine hospital data and follow up at day 28.

10.6.1.4 Eligibility criteria

Cluster level inclusion criteria

- >20 admissions with AUGIB per month
- > 400 hospital beds
- Availability of 24 hours endoscopy and on-site access to intensive care and surgical support
- Institutional agreement to transfuse all eligible new admissions with AUGIB in accordance with the randomised transfusion policy

Patient level inclusion criteria

- Adults aged ≥ 18 years presenting with AUGIB, defined by haematemesis or melaena.

Patient-level exclusion criteria

- Patients for whom the responsible clinician considered a need for immediate RBC transfusion prior to obtaining or regardless of the initial Hb result due to severity of bleeding
- Existing hospital in-patients who developed an AUGIB

10.6.1.5 Interventions

The trial compared two different policies for RBC transfusion.

Restrictive transfusion policy

- Patients in hospitals allocated to this group received transfusion if their Hb level was ≤8 g/dL. The objective for the attending clinician was to maintain the Hb level between 8.1-10 g/dL

Liberal transfusion policy

- Patients in hospitals allocated to this group received transfusion if their Hb level was ≤10 g/dL. The objective for the attending clinicians was to maintain the Hb level between 10.1-12 g/dL

10.6.1.6 Outcome Measures

Feasibility outcomes:

- Adherence to the study protocol
- Selection bias (clinical characteristics of patients in the two transfusion policies)
- Recruitment rate (the proportion of eligible patients enrolled into the study)
- Red blood cell exposure
- Difference in Hb concentration
- Information to guide the design of the Phase III trial by providing data to:

a) Enhance estimates of the intraclass correlation co-efficient

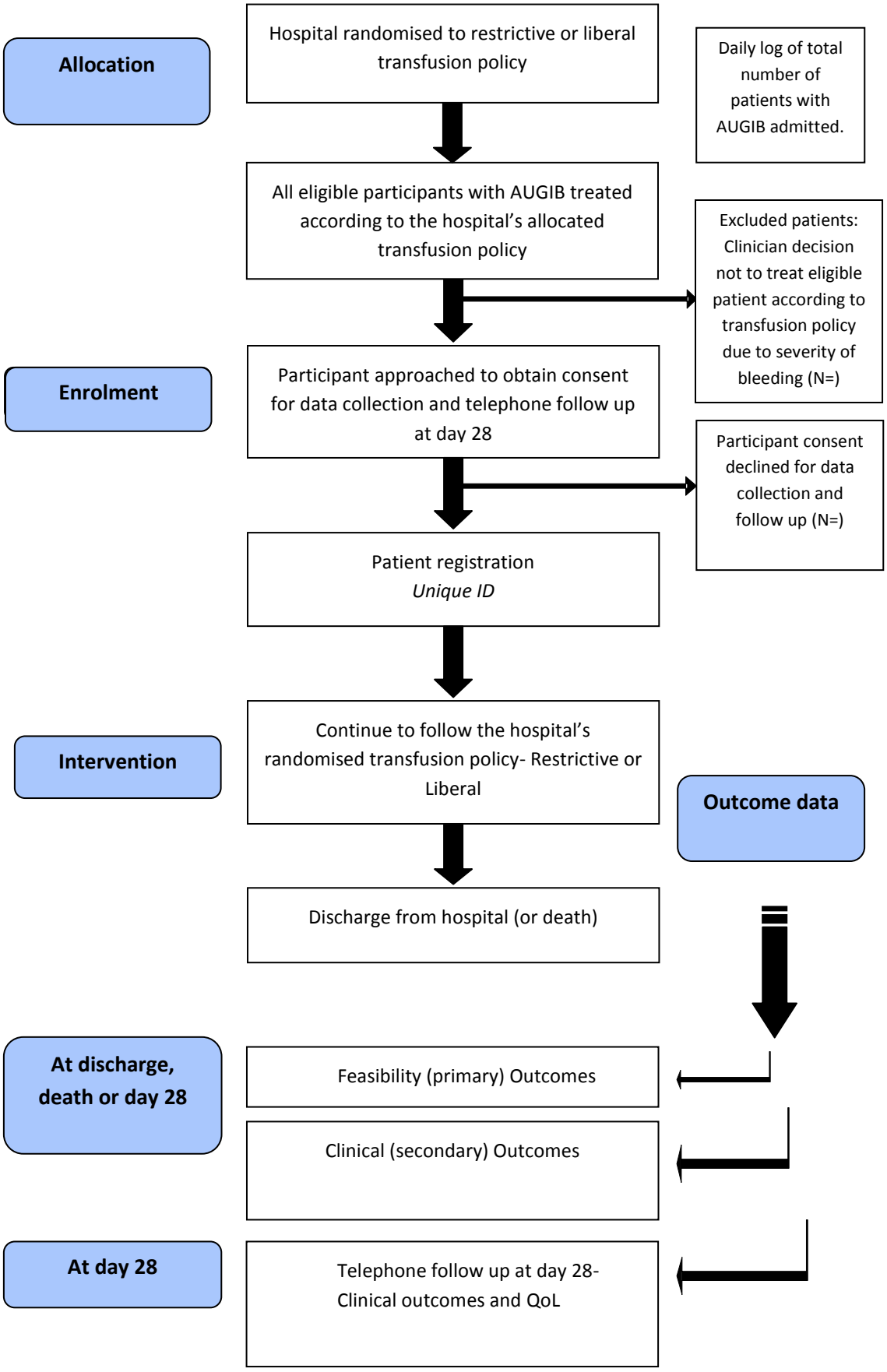
b) Identify factors leading to contraventions of the transfusion policy

- Information to guide the design of the economic evaluation of the Phase III trial

Clinical outcomes included:

- Further bleeding
- Death
- Need for therapeutic intervention at index endoscopy
- Need for surgery or radiological intervention to control bleeding
- Composite endpoint of thromboembolic and ischaemic events
- Transfusion reactions
- Infections
- Length of hospital stay
- Health related quality of life at Day 28 (Using EuroQol EQ-5D)

Figure 10.1 Participant screening and selection



10.6.2 National audit of blood transfusion in liver cirrhosis

Building upon the work outlined in Chapters 7 and 8 there is a need to characterise and rationalise the use of blood components in patients with liver cirrhosis. In 2012-2013, I proposed and developed a large national observational study in collaboration with NHSBT, representatives from the BSG and regional transfusion committees throughout the UK. All NHS hospitals have been invited to participate in the initiative. At the time of writing (March 2013), 109 hospitals have signed up to this initiative and are submitting cases on an on-line data collection tool.

Each hospital will submit details of all consecutive patients hospitalised with liver cirrhosis over a four week period and further details of those who receive any blood component during admission. The aims of the study are to:

- Describe contemporary current patterns of use all blood components in patients with liver cirrhosis and relate these to current standards and national guidelines.
- Obtain information on use of standard coagulation tests and other measures of haemostatic variables before and after transfusion.
- Present the data to participating hospitals for comparative purposes and produce recommendations to support hospitals in the appropriate use of blood components in liver cirrhosis.

10.6.3 The "HALT-IT" trial

In Chapter 8 it was demonstrated that patients with AVH have excessive fibrinolysis and *ex vivo* supplementation of whole blood with an antifibrinolytic was able to improve fibrinolysis and overall clot strength on ROTEM. Excessive fibrinolysis may play an important role both in the failure to control initial bleeding and in the precipitation of further bleeding through premature breakdown of blood clots at sites of vascular injury. This raises the possibility that an antifibrinolytic drug administered following AVH could limit severity of bleeding and transfusion requirements.

Tranexamic acid (TXA) is an antifibrinolytic drug which reduces clot breakdown by inhibiting the action of plasmin. It is commonly given to patients either before or during surgery to reduce bleeding and the need for blood transfusion. It has been shown to reduce mortality in bleeding trauma patients. The CRASH-2 trial, which enrolled 20,211 patients from hospitals in 40 countries, showed that administration of TXA within 8 hours of injury reduces deaths due to bleeding (RR=0.85, 95% CI 0.76 to 0.96), and all-cause mortality (RR=0.91, 95% CI 0.85 to 0.97) compared to placebo, with no apparent increase in thromboembolic events (The CRASH-2 Collaborators, 2010). As a consequence of the CRASH-2 trial results, TXA has been incorporated into trauma treatment protocols worldwide and is included on the WHO List of Essential Medicines.

These observations led to the hypothesis that TXA may be effective in the management of gastrointestinal bleeding. Since 2010, from the conception of the study, I have worked closely with the team who conducted the CRASH-2 trial at the London School of Hygiene and Tropical Medicine Clinical Trials Unit to develop the trial proposal, successful funding application (*NIHR HTA* Clinical Trials and Evaluation Board;

£3.1m), protocol development and site selection for the HALT-IT trial ("Haemorrhage alleviation with tranexamic acid – intestinal system") as a co-applicant and part of the Trial Management Group.

HALT-IT is a large, pragmatic, randomised, double blind placebo controlled trial which will aim to recruit 8000 patients with clinically significant gastrointestinal bleeding internationally. It will determine the effect of TXA on mortality, morbidity, blood transfusion, surgical intervention and health status in patients with acute gastrointestinal haemorrhage (including patients with liver cirrhosis and AVH). Recruitment will commence in the UK in July 2013.

10.7 Conclusions

The incidence of AUGIB is likely to increase in coming years driven by an ageing population, increasing use of NSAIDS, single or multiple anti-thrombotic agents, novel anticoagulants which do not have reversal agents, and the UK epidemic of liver cirrhosis. Improving outcomes requires a focus upon those patients in whom further bleeding and death is preventable. This will require education of frontline care providers to adhere to simple interventions proven to reduce death, through investment in services to ensure timely access to endoscopy for high risk patients and through training of endoscopists to ensure proficiency in all modalities of haemostasis. As the focus of clinical trials in AUGIB moves away from endoscopy, trials in progress will provide novel data on the safety and effectiveness of haemostatic interventions of blood component therapy and antifibrinolytics, all of which have the potential to further improve outcomes in patients with severe bleeding.

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Appendices

Appendix A: Ethical approval letter for laboratory study

Outer West London REC
Level 7 Maternity, Room 019
Northwick Park Hospital
Watford Road
Harrow
HA1 3UJ

Telephone: 020 8869 3928
Facsimile: 020 8869 5222

15 March 2010

Dr Vipul Jairath
Clinical research fellow in Gastroenterology
National Blood Service
John Radcliffe Hospital,
Headley Way
Headington
OX3 9BQ

Dear Dr Jairath

Study Title:	**Activation of Coagulation and inflammation in Acute Upper Gastrointestinal Bleeding- A Pilot Clinical Investigation.**
REC reference number:	**10/H0709/14**
Protocol number:	**1.1**

Thank you for your letter of 25th February and subsequent e-mail correspondence responding to the Committee's request for further information on the above research and submitting revised documentation. The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005
I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable)

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*	
Covering Letter		13 January 2010	
REC application	1	13 January 2010	
Investigator CV		13 January 2010	
Participant Information Sheet: legally appointed representative	1	13 January 2010	
Participant Information Sheet: for patient	1	13 January 2010	
Participant Consent Form: Legally appointed representative	1	13 January 2010	
Participant Consent Form: for patient	1	13 January 2010	
CV Dr. J. Vipul		13 January 2010	
Participant Information Sheet: Qualifying Relative/Nominated Representative for use of blood samples of deceased - Info Sheet F	1.1	23 February 2010	
Participant Information Sheet: Qualifying Relative/Nominated representative for use of blood samples of deceased - Info Sheet E	1.1	23 February 2010	
Participant Information Sheet: Consultee - Info Sheet C	1.1	23 February 2010	
Response to Request for Further Information			

Protocol	1.1	23 February 2010	
Covering Letter		25 February 2010	
Participant Information Sheet: Info Sheet A	1.1	23 February 2010	
Participant Information Sheet: Consultee - Info Sheet C			
Participant Information Sheet: Info Sheet B	1.1	23 February 2010	
Participant Information Sheet: for patient who regain capacity to consent during the study period - Info Sheet D	1.1	23 February 2010	
Participant Consent Form: Consent form A	1.1	23 February 2010	
Participant Consent Form: for patients who regain capacity to consent during the study period - Consent Form D	1.1	23 February 2010	
Participant Consent Form: Consent Form B	1.1	23 February 2010	
Consultee - Assent Form C	1.1	23 February 2010	
Response to Request for Further Information			

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0709/14	**Please quote this number on all correspondence**

Yours sincerely

Dr Jan Downer
Chair

Appendix B: Participant Information Sheet

Oxford Radcliffe Hospitals NHS
NHS Trust

PATIENT INFORMATION SHEET
NHS BLOOD AND TRANSPLANT
JOHN RADCLIFFE HOSPITAL, OXFORD, OX3 9 BQ

Information Sheet A- Version 1.1, 23/02/2010

Outer West London Research Ethics Committee
REC number: 10/H0709/14

Title: Activation of Coagulation and Inflammation in Acute Upper Gastrointestinal Bleeding
Chief Investigator: Dr Vipul Jairath
Academic Supervisor: Professor Mike Murphy

Date:

Participant Name: NHS Ref: Study Ref:

Introduction:
You are being invited to take part in a research study. Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully. Please ask us of there is anything that is not clear to you or if you need any further information. Take time to decide whether or not you wish to take part in this study.

Why have I been selected?
You have presented to hospital with symptoms of vomiting blood, or passing altered blood from the bottom end. These symptoms suggest that you are bleeding internally somewhere in your stomach or oesophagus (gullet). A common cause for this is, for example, an ulcer. This term medically is called “Acute Upper Gastrointestinal Bleeding” and is a common cause for hospital admission. You are likely to require a camera test (endoscopy) to identify and control the source of bleeding. At the time you were admitted you were unable to be approached to obtain informed consent. As part of the initial blood tests that were taken by the doctors who first admitted you, a small amount of extra blood (the equivalent of 4 teaspoons) was drawn and saved for research purposes. We are now asking for your consent to allow us to use the samples we have collected and to continue to participate in the study, since all of the procedures have not yet been completed.

Why is this research being carried out?
Although most people who present with Acute Upper Gastrointestinal Bleeding will recover well from this, in some instances the bleeding can be very severe and patients can be become

very unwell. Overall, 1 in 10 patients admitted to hospital in the UK with this condition die. This can be a result of severe bleeding or the complications resulting from it. Blood loss and shock can contribute to a failure of the body's blood clotting mechanisms, which can lead to further bleeding. The mechanisms of these disorders in blood clotting and how they affect the body are not well understood, and we hope that this research will help us understand the nature of the blood clotting disorder in this condition and what the consequences of this are.

Do I have to take part?

No. Participation is completely voluntary. It is entirely your decision whether or not you wish to take part in the study. If you do you will be given this information sheet to keep and be asked to sign a consent form. You are still totally free to withdraw at any time and do not have to give any reason. Whether or not you decide to take part in this study, the care you receive will not be altered in any way at all.

What will happen to me if I take part?

If you agree to take part in the study the following will happen:

1. We store and process the sample we have already taken.

2. We will collect some additional blood samples until the 3rd day of your hospital stay. We will draw …. further blood samples in total. Each blood sample is the equivalent of four teaspoonfuls. Where possible we will draw the blood out of line that is already in a blood vessel (cannula), or try to coincide the blood tests with the routine tests which your doctor would normally take. In this way we can minimise the number of blood tests that you have.

3. We will take blood tests of the following dates and time…….

What are the risks of taking part in the study?

There are no long-term risks to you from taking part in this study. Your normal course of care would not be altered in any way. The only specific risk is that of taking a blood sample. This includes temporary discomfort from the needle stick and potential bruising

What are the benefits of taking part in the study?

There is no direct benefit to you during this admission if you decide to participate in this study. However, we hope that the information we get will help the care of patients in the future who present with this condition.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2.

This Completes Part 1.

If the information in Part 1 has satisfied you and you are considering continuing in the study, please read the additional information in Part 2 before making any decision.

PART 2

What happens if I agree to take part now, but then decide to withdraw?

You are free to withdraw from the study at any time and do not need to give any explanation to do so. If this is the case all study procedures will be stopped immediately. Any information and samples that have already been collected will be processed as part of the study unless you wish to have your samples withdrawn. In no way will the type or quality of care you receive change if you withdraw from the study.

What happens if I am not happy about the study?

At no point will your normal course of care be altered by taking part in this study. The only way in which your care will be slightly altered is by taking some extra blood samples. It is extremely unlikely that this will cause any problems. However, if you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone negligence then you may have grounds for legal action but you may have to pay for your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism will be available to you. Please contact the Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 01865 221473, or email PALSJR@orh.nhs.uk. You can also visit PALS by asking at any hospital reception.

Will my taking part in the study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential and securely stored in a coded format. Data may be sent outside the trust for statistical analysis, but any uncoded identifiable personal patient information will not leave the local research group. If you do consent to taking part in the research the individuals conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. Only authorised personnel such as researchers and research auditors will have access to the data. We will store your information for 3 years and your blood samples until the end of this research project. Any subsequent use of these samples will have to be performed with further approval form a research ethics committee, otherwise the samples will be destroyed.

What will happen to the samples that I give?

Your blood samples will be stored within a secure facility that can only be accessed by authorised researchers. It is anticipated that all samples will be analysed within the trust. In the event that samples need to be sent outside the trust for analysis, your samples will be identifiable only in a coded format separate from your personal information. At the end of the study the samples will be disposed in accordance with the Human Tissue Authority's Code of Practice.

What will happen to the results of the research study?

The blood tests that we will take are special laboratory tests. The results will not be immediately available, but any results that could be helpful will be shared with the medical team caring for you. We hope to publish the results in a scientific journal. It will not be possible

to identify any individual who has taken part from this scientific report. Copies of this report will be available on request.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people known as a Research Ethics Committee. This committee protects your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by.....

Who can I contact for further information?

If you require further information about the study please contact the study author via the National Blood Service on 01865 447 908 or email Dr Vipul Jairath at: Vipul.Jairath@nhsbt.nhs.uk

If you require impartial, local advice, please contact the Patient Advice and Liaison Service, telephone 01865 221473 or email: PALSJR@orh.nhs.uk

Thank you for taking the time to read this sheet.

Date: **Researcher Signature:**

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