SUPPLEMENTARY FILE

REJECTED STATEMENTS

The following statements were drafted by the AUGIB bundle development group and subjected to the evidence review, drafting and Delphi voting process. In the round of voting for inclusion in the final bundle these statements were rejected, either because there was insufficient evidence to support inclusion or to avoid unnecessary duplication of the process of care in patients in whom the bundle item might be applied. Finally, the group rejected statements for bundle items which are not already standard of care in UK and European hospitals to ensure generalisability of the bundle in clinical practice.

1. We suggest digital rectal examination (DRE) is performed in patients with suspected AUGIB who do not have haematemesis, coffee ground vomiting or melaena.

Level of evidence:	Very Low
Level of recommendation:	Weak
Agreement:	50% Agreement (Rejected)

Traditionally, DRE has been an established part of the physical examination in patients with suspected AUGIB, although its impact on subsequent clinical management is unclear. Based on one retrospective analysis of 1237 patients with suspected upper or lower gastrointestinal bleeding, DRE was associated with reduced multivariate odds for admission (OR 0.49, P=0.004), initiation of medical therapy (OR 0.64, p=0.04), inpatient endoscopy (OR 0.64, P=0.02), but not the need for ICU admission (OR 1.35, p=0.10), transfusion (p=0.26) or gastroenterology consultation (p=0.84). The authors proposed that, in the context of gastrointestinal bleeding, DRE can assist clinicians with clinical management decisions and can potentially reduce the need for endoscopy, admission and medical therapy. However DRE was only performed in 55.6% of patients in this study. [106] Increasingly, clinicians are reluctant to perform a rectal examination.[107] Due to concerns over clinician and patient acceptability and the lack of evidence to support DRE, the statement was rejected.

2. Inpatients with AUGIB are at higher risk of mortality. In such patients, we recommend early recognition, resuscitation and escalation to involve a senior clinician.

Level of evidence:	Low
Level of recommendation:	Strong
Agreement:	40% Agreement (Rejected)

Patients who develop AUGIB when hospitalised for another condition have at least a 3-fold increase in mortality compared to those admitted with AUGIB [108-110]. Reasons for this include increasing age, co-morbidities, coagulopathy, in addition to greater severity of bleeding and higher incidence of re-bleeding [111]. As the group consensus was for management to be standardised for all patients with AUGIB, and evidence for the benefit of senior review was not available, this statement was rejected.

3. We suggest shock index be measured at presentation and used as a marker of adequacy of resuscitation.

Level of evidence:	Very Low
Level of recommendation:	Weak
Agreement:	0% Agreement (Rejected)

The shock index (SI), heart rate divided by systolic blood pressure, can easily be calculated at the point of admission without the need for laboratory-based parameters. However, the evidence for using SI in AUGIB to measure resuscitation status is limited. There are no randomised controlled trials (RCTs) comparing SI with other measures (BP, Heart rate, Glasgow Coma Scale, urine output) and none of the well validated risk assessment scores in AUGIB use SI. Studies in AUGIB have shown that SI was inferior to other risk scores in predicting transfusion requirements,[112,113] critical care admission,[112] endoscopic therapy [113] and mortality.[112,113] The group consensus was to reject SI in favour of GBS which had greater evidence in predicting adverse outcome.

4. In specific situations where non-variceal upper GI bleeding is suspected, e.g. patients with haemodynamic instability, or if there is likely to be a delay in endoscopy, we suggest considering intravenous PPI prior to endoscopy.

Level of evidence:	*Moderate*
Level of recommendation:	*Weak*
Agreement:	40% Agreement (Rejected)

Several studies have evaluated the role of pre-endoscopic PPI administration in NVUGIB. A pilot RCT from Hong Kong assigned 638 patients to omeprazole infusion or placebo.[114] Pre-endoscopic PPI was associated with reductions in stigmata of active bleeding and endotherapy, but no difference in transfusion requirements, rebleeding, surgical intervention or 30-day mortality. A meta-analysis of 6 RCTs (N=2223) compared PPI (oral or intravenous) to control treatment with either placebo, histamine-2 receptor antagonist or no treatment prior to endoscopy.[115] The PPI arm was associated with reduced need for endoscopic therapy, but not mortality, re-bleeding or surgery.

The NICE guidelines do not advocate pre-endoscopic PPI administration in patients with suspected AUGIB.[5] ESGE guidelines recommend initiating bolus followed by continuous PPI infusion in patients

presenting with AUGIB awaiting upper endoscopy, but emphasised that PPI infusion should not delay the performance of early endoscopy.[6]

The bundle development group recognises that in UK clinical practice, PPIs are often administered before endoscopic therapy. The 2007 UK audit found that 48% of patients with AUGIB (including those who did not undergo endoscopy) received PPI therapy, of which 89% were commenced prior to endoscopy.[2] Outcomes regarding PPI were not presented. This statement was therefore rejected in view of the lack of evidence of benefit for outcomes in patients with AUGIB and as it is consistent with current UK guidelines.

5. We suggest giving IV erythromycin to all patients with AUGIB who need emergency endoscopy and are having ongoing hematemesis.

Level of evidence:	*High*
Level of recommendation:	Weak
Agreement:	30% Agreement (Rejected)

Prokinetics may have a role in improvement mucosal visualisation, particularly in patients with ongoing haemorrhage or if there are concerns regarding the nil by mouth window. The evidence for pre-endoscopic erythromycin in AUGIB is supported by a meta-analysis of 6 RCTs which compared intravenous erythromycin vs no erythromycin [116]. Pre-endoscopic erythromycin was associated with improved visualization of the gastric mucosa and reductions in the need for a second endoscopy, blood transfusion and length of hospital stay.

Another meta-analysis evaluated 4 RCTs (N=335) involving erythromycin in AUGIB.[117] The dosage of erythromycin ranged from 3mg/kg to 250mg with endoscopy performed 20-30 min after erythromycin infusion. The primary outcome of incidence of empty stomach was higher with erythromycin use (69% vs. 37%, P<0.001). Secondary outcomes comprised the need for second endoscopy, amount of blood transfusion and the length of hospital stay, which were significantly lower in the erythromycin arm. A trend towards shorter endoscopic procedure time and lower mortality rates were observed.

ESGE recommends intravenous erythromycin (single dose, 250mg given 30-120 minutes prior to upper GI endoscopy) in patients with clinically severe or ongoing active AUGIB,[6] on the grounds that, in selected patients, pre-endoscopic infusion of erythromycin significantly improves endoscopic visualization, reduces the need for second-look endoscopy, decreases the number of units of blood transfused, and reduces duration of hospital stay.

Whilst the level of evidence for this statement was high, the bundle development group felt that IV erythromycin is likely to be useful in selected patients only and the decision on administration and timing of IV erythromycin should be at the discretion of the endoscopist carrying out emergency endoscopy and not to be mandated within the bundle.