NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2018 surveillance of acute upper gastrointestinal bleeding in over 16s: management (NICE guideline CG141)

Proposed surveillance decision

We propose to not update the NICE guideline on acute upper gastrointestinal bleeding.

We considered this guideline alongside the following related guidelines:

- Gastro-oesophageal reflux disease in children and young people: diagnosis and management (NICE guideline NG1)
- Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (NICE guideline CG184)
- Barrett's oesophagus: ablative therapy (NICE guideline CG106)

Separate consultations on the surveillance decisions for the guidelines on GORD in adults and GORD in children and young people are underway. See the webpages for each guideline to participate in consultation on these guidelines.

We propose to fully update the guideline on Barrett's oesophagus so we are not conducting public consultation on the surveillance decision for that guideline. See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Reasons for the proposal to not update the guideline

We found new evidence on tools for assessing risk of poor outcomes after acute upper gastrointestinal bleeding (mainly AIMS65, Blatchford and Rockall). Evidence indicated that no tool appears to be sufficient to be used alone; which is consistent with the current recommendation to use both the Blatchford score and the Rockall score after endoscopy.

Evidence on resuscitation and initial management was generally consistent with current recommendations. Two randomised controlled trials suggested benefits of tranexamic acid after acute upper gastrointestinal bleeding. However, effects were not consistent across outcomes, and no effect on mortality was seen. We are awaiting results of the ongoing HALT-IT study. This NIHR-funded study aims to study the effects of tranexamic acid in

12,000 people with acute gastrointestinal bleeding. When results from this study are published we will assess the impact on the guideline.

We found several studies looking at oral compared with intravenous administration of proton pump inhibitors (PPIs) for non-variceal bleeds. Overall, there appeared to be little difference between the methods, although results were inconsistent between studies. Therefore, we decided that the case was not strong enough for an update to cover routes of administration for PPIs.

A large number of new studies covering various interventions, comparators and outcomes for variceal bleeding were identified. Results were inconsistent across interventions and outcomes. However, overall, band ligation and TIPS appear to be effective for oesophageal varices. Similarly, cyanoacrylate and TIPS appear to be effective for gastric varices. These findings support current recommendations for treating variceal bleeding. There was no strong indicator of a need to update to consider other interventions for variceal bleeding.

Evidence indicated that stress ulcer prophylaxis appears to reduce gastrointestinal bleeding, and there was no consistent evidence of increased infections. These findings support the current recommendations to offer acid suppression therapy as stress ulcer prophylaxis in people admitted to critical care.

For further details and a summary of all evidence identified in surveillance, see appendix A below.

Overview of 2018 surveillance methods

NICE's surveillance team checked whether recommendations in acute upper gastrointestinal bleeding in over 16s: management (NICE guideline CG141) remain up to date.

The surveillance process consisted of:

- Initial feedback from topic experts via a questionnaire.
- Input from stakeholders on known variations in practice and policy priorities.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations and deciding whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the decision with stakeholders (this document)
- Consideration of comments received during consultation and making any necessary changes to the decision.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

See appendix A: summary of evidence from surveillance below for details of all evidence considered, with references.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline. We found 78 studies in a search for randomised controlled studies, systematic reviews, and observational studies published between 1 April 2016 and 7 June 2018.

We also included a total of 18 studies identified by search in previous surveillance in 2016 and the 2014 Evidence Update.

From all sources, we considered 86 studies to be relevant to the guideline.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 2 studies were assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Haemorrhage alleviation with tranexamic acid intestinal system (HALT-IT)
- Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU)

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to NICE guideline CG141. We sent questionnaires to 8 topic experts and received 2 responses. The topic experts either:

- participated in the guideline committee who developed the guideline
- were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

Topic experts highlighted the ongoing HALT-IT trial, which we will check regularly for publication.

Topic experts drew attention to a topical haemostatic known as Hemospray. One small study in 86 people suggested benefit of Hemospray plus endoscopy compared with endoscopy alone. However, Hemospray is delivered by endoscopy, so if it was used as in the trial, it would lead to an additional endoscopic procedure. Its role in UK practice is unclear because

the study did not assess Hemospray compared with, or added to, other treatments delivered at endoscopy.

The guideline investigated the balance between the risks of continuing aspirin treatment (increased risk of bleeding and prolonging bleeding) and the risks of stopping aspirin (stroke or myocardial infarction). It recommended continuing low-dose aspirin in patients in whom haemostasis has been achieved. tTopic experts suggested that aspirin may be withheld for a few days after upper gastrointestinal bleeding in some services in the UK. This suggests that the recommendation may not be fully followed. However, we did not identify any evidence that could improve adherence to the recommendation.

Topic experts additionally suggested that the guideline should cover use of non-vitamin K oral anticoagulant drugs. The guideline assessed the antiplatelet agents aspirin and clopidogrel because their irreversible inhibition of platelets means that their action lasts for around 10 days after stopping treatment. Evidence identified in surveillance suggested that the benefits of continuing oral anticoagulants after a major bleeding event, including upper gastrointestinal bleeds, outweigh the risks of future bleeds. Therefore, updating recommendations to include advice on anticoagulants was not thought to be necessary at this time.

Views of stakeholders

Stakeholders are consulted on all surveillance decisions except if the whole guideline will be updated and replaced. Because this surveillance decision was to not update the guideline, we are consulting on the decision.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary.

Appendix A: Summary of evidence from surveillance

2018 surveillance of dyspepsia – acute upper gastrointestinal bleeding (2012) NICE guideline CG141

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a final decision on the need to update each section of the guideline.

Risk assessment

1.1.1 Use the following formal risk assessment scores for all patients with acute upper gastrointestinal bleeding:

- the Blatchford score at first assessment, **and**
- the full Rockall score after endoscopy.

1.1.2 Consider early discharge for patients with a pre-endoscopy Blatchford score of 0.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

Previous surveillance in 2016, identified no relevant evidence. In an Evidence Update in 2014, new evidence from 1 study (1) was consistent with current recommendations to use both the Blatchford and Rockall scores.

2018 surveillance summary

We identified 14 studies that evaluated risk assessment tools.

Table 1 at the end of this section summarises the results of 10 studies reporting standard measures such as the area under the curve (AUC), sensitivity and specificity. Additional results from the studies in the table are as follows:

- In one study (2), the authors concluded that no assessed score was helpful for predicting rebleeding or length of stay. Optimum cut-offs for other outcomes were:

  - A Blatchford score ≤1 for survival without intervention had sensitivity of 99% and specificity of 35%.
  - A Blatchford score ≥7 for need for endoscopy had sensitivity of 80% and specificity of 57%.
  - Score thresholds of ≥4 for Progetto Nazionale Emorragia Digestiva (PNED), ≥2 for AIMS65, ≥4 for admission Rockall, and ≥5 for full Rockall were optimum for predicting death, with sensitivities of 66–79% and specificity of 65%.
- In one study (3), the optimum score for detecting patients at low risk of adverse outcomes was the Glasgow Blatchford score with a cut-off of 0, which had sensitivity of 99% and specificity of 8%.
- In one study (4) the composite endpoint of severity, transfusion requirements, rebleeding, delayed (6-month) mortality was assessed. High-risk patients were identified by a Blatchford score of ≤1 or Rockall score of ≤2, but not by an AIMS65 score of 0.
- In one study (5), of the 4 scores assessed, only the post-endoscopy Rockall score achieved significance in identifying rebleeding (AUC 68%). All four scores accurately predicted risk in patients with non-variceal bleeds; however, only the Blatchford score (and the modified version) were useful for risk prediction in variceal bleeds. The optimum cut-off scores were:
  - Pre-endoscopy Rockall score of 0 (sensitivity 50%, specificity 61%).
  - Complete Rockall score of >1 (sensitivity 86%, specificity 51%).
  - Blatchford score of >7 (sensitivity 89% and specificity 63%).
  - Modified Blatchford score of >7 (sensitivity 82%, specificity 73%).
- In one study (6), people assessed as at high risk by any scoring tool had higher rates of rebleeding, intervention and death compared with the low-risk groups.

The remaining 4 studies reported other measures or assessed other risk assessment methods.

A Mexican cross-sectional study (7) assessed the Rockall score and the Italian Progetto Nazionale Emorragia Digestiva (PNED) score in 198 people with non-variceal upper gastrointestinal bleeding. Overall, 8 patients (4%) died from causes directly associated with bleeding. According to the Rockall score, 46 patients (23.2%) had severe disease, 5 of whom died. PNED classed 8 patients as having severe disease (4%), 5 of whom died.

A prospective cohort study (8) assessed 4 risk assessment tools (Rockall, Blatchford, modified Blatchford and AIMS65) in 129 people with upper gastrointestinal bleeding. The Blatchford score had the highest sensitivity and negative predictive value; however the authors noted that it 'could not achieve' good specificity and positive predictive value. The Blatchford score and the modified Blatchford score outperformed the Rockall and AIMS65 scores in predicting 'composite high-risk outcome', length of stay in hospital and blood transfusion.

A retrospective study (9) assessed the use of the delta neutrophil index in 432 people with upper gastrointestinal bleeding. Higher delta neutrophil index values at

days 0 and 1 were associated with short-term mortality. Mortality was higher in people with a delta neutrophil index value greater than 1% on admission, and the optimum cut-off for predicting mortality was a value of 2.6% on day 1.

One randomised controlled trial (10) assessed Doppler probe monitoring of blood flow compared with no Doppler monitoring during endoscopy for severe non-variceal upper gastrointestinal bleeding (n=148). Doppler monitoring was associated with significantly lower rates of rebleeding within 30 days. Treating 7 people could prevent one rebleed.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

The two scores that were most frequently compared were the Rockall score and the Blatchford score. The Rockall score had an AUC ranging from 57% to 84%, which varied by population, by outcome, and by conducting before or after endoscopy.

The Blatchford score had an AUC ranging from 52% to 83%. Again this varied by population, by outcome and whether the original or modified versions of the score were used. The range of AUC values suggests the ability of these tests to detect people likely to have poor outcomes may range from poor to good.

The low AUC values appear to be driven by low specificity, whereas, sensitivity is high. For people with upper gastrointestinal bleeding, sensitivity is most important to avoid missing people who go on to have further bleeding.

The evidence is consistent with the guideline in that neither of these tests appears to be sufficient on its own.

The AIMS65 test did not appear to be more accurate than either the Rockall score or the Blatchford score. Other tests such as PNED, were studied less often, but again did not appear to have increased accuracy. Therefore, there is insufficient evidence suggesting a need to update the current recommendations to use the Blatchford score before endoscopy and the Rockall score afterwards.

When cut-off values for the Rockall score and the Blatchford score were assessed, the optimum score was influenced by the outcome evaluated. Higher cut-off scores appeared to increase specificity at the expense of sensitivity. Because sensitivity is more valuable in this population, the evidence was consistent with the current recommendation to consider discharging people with a pre-endoscopy Blatchford score of 0.

Two new strategies were identified. Both the delta neutrophil index and Doppler monitoring show promise for identifying risk in people with upper gastrointestinal bleeding. However, neither of these studies compared the new strategy with either of the established risk scoring tools (Blatchford or Rockall scores). Therefore, an update to evaluate these new strategies is not thought to be needed at this time.

New evidence is unlikely to change guideline recommendations.

Table 1 Summary of risk assessment tool studies

Study	n	Predicted outcome	Score			
			AIMS65	Blatchford	Rockall	Other
Ramaekers 2016 (3)	16 studies	Composite of 30-day mortality, rebleeding, and intervention	Sensitivity 79% Specificity 61%	Sensitivity 98% Specificity 16%	Sensitivity 93% Specificity 24%	–
Kayali 2017 (11)	188	Unclear	–	Sensitivity 96% Specificity 10%	Sensitivity 74% Specificity 46%	–
Motola-Kuba 2016* (12)	160	Rebleeding	AUC 82%	AUC 76%	AUC 69%	MELD AUC 83%
Wang 2017 (13)	234	Endoscopy	–	AUC 63%	AUC 60%	–
		Rebleeding	–	AUC 69%	AUC 58%	–
Stanley 2017 (2)	3,012	Intervention or death	AUC 68%	AUC 86%	AUC 70% (CRS) AUC 66% (PRS)	PNED AUC 69%
		Endoscopy	AUC 62%	AUC 75%	AUC 61%	–
		Death	AUC 77%	AUC 64%	AUC 72%	PNED AUC 77%
Martinez-Cara 2016 (4)	309	In-hospital mortality	AUC 76%	AUC 78%	AUC 78%	–
		Endoscopy	AUC 62%	AUC 62%	–	–
		Rebleeding	AUC 56%	AUC 70%	AUC 71%	–
Anchu 2017 (5)	175	Overall risk	–	AUC 81% AUC 80% (mGBS)	AUC 71% (CRS) AUC 57% (PRS)	–
		30-day mortality	–	AUC 83% AUC 82% (mGBS)	AUC 80% (CRS)	–
Thanapirom 2016 (14)	225 (variceal)	Intervention	–	AUC 66%	AUC 66% (CRS) AUC 59% (PRS)	–
		In-hospital mortality and rebleeding	–	AUC 63%	AUC 57% (CRS) AUC 63% (PRS)	–
	756 (non-variceal)	Intervention	–	AUC 77%	AUC 69% (CRS) AUC 61% (PRS)	–
		In-hospital mortality and rebleeding	–	AUC 66%	AUC 80% (CRS) AUC 70% (PRS)	–
Budimir 2017 (15)		Death	–	AUC 63%	AUC 82% (PRS) AUC 82% (CRS)	BBS (pre) AUC 67% BBS (post) AUC 69%

Study	n	Predicted outcome	Score			
			AIMS65	Blatchford	Rockall	Other
	Unclear (peptic ulcer only)	Intervention or 30-day mortality	–	AUC 64%	AUC 84% (PRS)	BBS (pre) AUC 57%
		Rebleeding	–	AUC 53%	AUC 75% (PRS)	BBS (pre) AUC 61%
		Surgery	–	AUC 52%	AUC 82% (PRS)	BBS (pre) AUC 63%
		Transfusion	–	AUC 58%	AUC 83% (PRS)	BBS (pre) AUC 63%
Zhong 2016 (6)	320	Rebleeding	AUC 74%	AUC 67% AUC 68% (mGBS)	–	–
		Intervention	AUC 75%	AUC 77% AUC 75% (mGBS)	–	–
		In-hospital mortality	AUC 79%	AUC 80% AUC 80% (m GBS)	–	–

n=number of participants, unless number of studies is specified, which is applicable to systematic reviews. PNED=Progetto Nazionale Emorragia Digestiva. AIMS65 (no definition identified). MELD=Model for end-stage liver disease.

AUC= area under the curve. CRS=Complete Rockall score. PRS=Pre-endoscopy Rockall score. mGBS= modified Batchford score. BBS=Baylor bleeding score (pre or post endoscopy).

*variceal bleeds only.

If no results were reported for a score or an outcome, the absent data are indicated by –.

Resuscitation and initial management

1.2.1 Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding.

1.2.2 Base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.

1.2.3 Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable.

1.2.4 Offer platelet transfusion to patients who are actively bleeding and have a platelet count of less than 50 x 10^9/litre.

- Offer fresh frozen plasma to patients who are actively bleeding and have a prothrombin time (or international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal. If a patient's fibrinogen level remains less than 1.5 g/litre despite fresh frozen plasma use, offer cryoprecipitate as well.

1.2.5 Offer prothrombin complex concentrate to patients who are taking warfarin and actively bleeding.

1.2.6 Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols.

1.2.7 Do not use recombinant factor VIIa except when all other methods have failed.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

Transfusion strategies

Previous surveillance in 2016 identified no evidence relevant to transfusion strategies. In an Evidence Update in 2014, evidence from 2 studies (16,17) was consistent with current recommendations to base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.

Tranexamic acid

A Cochrane review (18) of 7 studies assessing tranexamic acid in upper gastrointestinal bleeding was identified in the 2014 Evidence Update. Mortality was lower in people who received tranexamic acid, but there was no effect on bleeding or amount of blood transfused. An update (19) of this Cochrane review was identified in 2016 surveillance. This review included one additional study, but reached the same conclusions as the previous version of the Cochrane review.

The HALT-IT study of tranexamic acid in gastrointestinal bleeding was identified as

ongoing in the 2014 Evidence Update. This trial remains ongoing, and is expected to end in September 2020. We will consider the impact of this study on current recommendations when results are published.

2018 surveillance summary

Transfusion strategies

A systematic review (20) of 5 randomised controlled trials (n=1,965) assessed restrictive compared with liberal transfusion strategies in people with upper gastrointestinal bleeding. People had 1.73 fewer units of blood transfused in the restrictive transfusion group. Restrictive transfusion was associated with lower risk of all-cause mortality and rebleeding. No differences were seen for risk of ischaemic events or in the subgroups (variceal or non-variceal bleeding or presence of ischaemic heart disease).

Prophylactic nasogastric tube

A randomised controlled trial (21) assessed placing a nasogastric tube plus aspiration and lavage, compared with no nasogastric tube in people with upper gastrointestinal bleeding (n=280). Placing a nasogastric tube did not improve prediction of high-risk lesions or patients' outcomes, and complication arose in a third of patients.

Prophylactic intubation

A systematic review (22) of 10 observational studies (n=6,068) evaluating prophylactic endotracheal intubation compared with usual care in people with upper gastrointestinal bleeding. Studies in which participants mainly had respiratory indications for intubation were excluded. Prophylactic intubation was associated with higher rates of aspiration, pneumonia and increased length of stay in hospital. The effect on mortality was uncertain.

Tranexamic acid

A randomised controlled trial (23) assessed 1 g tranexamic acid delivered intravenously compared with topical delivery via nasogastric tube and with placebo in people with acute gastrointestinal bleeding (n=410). Need for urgent endoscopy was lower in the two tranexamic acid groups compared with placebo. No differences were seen between treatment groups for mortality, rebleeding, transfusion, and endoscopic or surgical intervention rates.

A further randomised controlled trial (24) assessed topical tranexamic acid (1 g via nasogastric tube) compared with placebo (n=131). People receiving topical tranexamic acid had less blood transfused, fewer rebleeds, and fewer emergency endoscopies. Mortality did not differ significantly between the groups.

Intelligence gathering

Topic experts have highlighted the importance of the HALT-IT study in all surveillance reviews and in the 2014 Evidence Update. This NIHR-funded study aims to study the effects of tranexamic acid in 12,000 people with acute gastrointestinal bleeding.

Topic expert feedback suggested that this section of the guideline should be updated to include advice on treatment for people using non-vitamin K oral anticoagulants,

Impact statement

A systematic review suggested that a restrictive blood transfusion strategy may

be associated with improved patient outcomes. This is generally consistent with current recommendations to base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.

Studies suggested no benefit and possible harm from prophylactic endotracheal intubation or insertion of a nasogastric tube. Neither of these interventions are currently recommended, and evidence is insufficient to trigger an update in this area.

Although topic expert feedback suggested that this section of the guideline should be updated to include advice on treatment for people using non-vitamin K oral anticoagulants, no new evidence was identified. Although one new drug treatment (idarucizumab), is available, it has a fairly restricted license and inhibits only one of the available the non-vitamin K oral anticoagulant drugs (dabigatran). Therefore, the appropriate treatment for most patients on these drugs would remain blood products such as platelets as currently recommended by the guideline.

Studies of tranexamic acid show inconsistent results, therefore, we will await results of the HALT-IT trial and then consider the impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Timing of endoscopy

1.3.1 Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation.

1.3.2 Offer endoscopy within 24 hours of admission to all other patients with upper gastrointestinal bleeding.

1.3.3 Units seeing more than 330 cases a year should offer daily endoscopy lists. Units seeing fewer than 330 cases a year should arrange their service according to local circumstances.

Surveillance decision

This section of the guideline should not be updated.

Erythromycin and gastric visibility

Previous surveillance

In previous surveillance in 2016, no evidence relevant to this issue was identified.

In the Evidence Update in 2014, new evidence from one systematic review (25) of 7 studies (n=558) showed that erythromycin administered before endoscopy was associated with increased visibility of gastric mucosa, reduced need for second endoscopy, shorter stay in hospital, and fewer units of blood transfused.

2018 surveillance summary

A systematic review (26) of 8 studies (n=598) assessed erythromycin administered before endoscopy compared with no erythromycin or placebo. The results remained broadly the same as the earlier systematic review – erythromycin was associated with increased visibility of gastric mucosa, reduced need for second endoscopy and shorter stay in hospital. No significant differences in duration of procedure, transfusion or need for surgery were seen.

Erythromycin does not have a UK marketing authorisation for this indication.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

Since the Evidence Update was published in 2014, the evidence base seen in the systematic reviews appears to have grown by one study of 40 people (from 7 studies, n=558 to 8 studies, n=598). Therefore, the conclusion of the Evidence Update, that these results need to be confirmed in a large randomised controlled trial, remains unchanged.

New evidence is unlikely to change guideline recommendations.

Helicobacter pylori testing

Previous surveillance

No relevant evidence was identified in previous surveillance in 2016, or in the 2014 Evidence Update.

2018 surveillance summary

A prospective study (27) assessed the diagnostic yield of dual-priming oligonucleotide-based multiplex polymerase chain reaction (DPO-PCR) compared with the rapid urease test and with histology for detecting *H pylori* infection in people with bleeding peptic ulcers (n=170). Biopsy samples were obtained during second endoscopy, and people with negative results had a second biopsy 8 weeks later. *H pylori*-was confirmed in 64% of the participants. At second endoscopy, histology had sensitivity of 48% and the rapid urease test had sensitivity of 72%. DPO-PCR had sensitivity of 97% and specificity of 92%. Its positive predictive value was 96% and negative predictive value was 95%. *H pylori*-associated bleeding was confirmed

in 64.1% of the patients. At the bleeding episode, the sensitivity of rapid urease test was, 48%, histology was 71.6% and DPO-PCR was 97.2%.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

DPO-PCR may be a useful test for *H pylori*, however, this study compared three invasive tests. It did not provide information to compare against the non-invasive tests recommended in Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (NICE CG184).

New evidence is unlikely to change guideline recommendations.

Weekend effect

Previous surveillance

No relevant evidence was identified in previous surveillance in 2016, or in the 2014 Evidence Update.

2018 surveillance summary

A systematic review (28) of 21 studies investigated the presence of a 'weekend effect' (an increase in mortality associated with admission to hospital at the weekend) in people with upper gastrointestinal bleeding. The number of participants was not reported in the abstract. There was a possible small increase in mortality with weekend admissions, but there was uncertainty in this effect.

Another systematic review (29) of 18 studies (n=1,232,083) assessed the weekend effect in people with upper gastrointestinal bleeding. This study found significantly higher in-hospital or 30-day mortality. A weekend effect resulting in increased mortality was seen for non-variceal bleeding but not for variceal bleeding. The time to endoscopy was shorter for weekday admission than for weekend admission.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

Two systematic reviews suggest a possible increase in mortality in people admitted with upper gastrointestinal bleeding at the weekend. This may affect people with non-variceal bleeds but not those with variceal bleeds. One study noted an increased time to endoscopy at the weekend.

Endoscopy is currently recommended either immediately after resuscitation for patients whose condition is unstable or within 24 hours for those whose condition is stable. Therefore, services providing endoscopy according to current guidance, should already have endoscopy available at weekends.

New evidence is unlikely to change guideline recommendations.

Management of non-variceal bleeding

Endoscopic treatment

1.4.1 Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.

1.4.2 For the endoscopic treatment of non-variceal upper gastrointestinal bleeding, use one of the following:

- a mechanical method (for example, clips) with or without adrenaline
- thermal coagulation with adrenaline
- fibrin or thrombin with adrenaline.

Previous surveillance

No relevant evidence was identified in previous surveillance in 2016, or in the 2014 Evidence Update.

2018 surveillance summary

A network meta-analysis (30) of 17 studies assessed treatments as an add-on to endoscopic adrenaline injection. 'Mechanical therapy' significantly reduced probability of rebleeding and surgery. 'Thermal therapy' significantly reduced probability of rebleeding but not surgery. Sclerosant therapy had no additional benefits and ranked highest for adverse events.

A randomised controlled trial (31) assessed addition of fresh frozen plasma to adrenaline injection compared with adrenaline injection alone (n=108). No significant differences were seen between the groups for achieving haemostasis, rebleeding, deaths, need for surgery, or length of stay in hospital.

A non-inferiority study (32) assessed second endoscopy after 16–24 hours plus bolus omeprazole every 12 hours compared with high-dose omeprazole infusion in people with bleeding peptic ulcers (n=153). Omeprazole was delivered for 72 hours in both groups. The margin for non-inferiority was set at 5%. No significant differences were seen for rebleeding or surgery for rebleeding. People in the second endoscopy group were discharged from hospital a day earlier than those in the omeprazole infusion group.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

Evidence suggests that mechanical and thermal endoscopic therapy in addition to adrenaline is beneficial. However, neither sclerosant therapy nor fresh frozen plasma appear to have any beneficial effects when

added to endoscopic adrenaline injection. The evidence is consistent with the current recommendations, which include several effective options including mechanical and thermal methods.

Current recommendations do not cover second endoscopies. Evidence from one study suggests that a proton pump inhibitor (PPI) administered as bolus plus second endoscopy could lead to earlier discharge from hospital compared with administration by infusion. However, the design of this study means that it is difficult to establish whether people were discharged earlier because second endoscopy gave additional information to support discharge or whether administration of the PPI by bolus was more effective than infusion.

New evidence is unlikely to change guideline recommendations.

Proton pump inhibitors

1.4.3 Do not offer acid-suppression drugs (proton pump inhibitors or H_2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.

1.4.4 Offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance summary

Previous surveillance in 2016 noted MHRA drug safety updates (April 2010, April 2012, April 2012 and September 2015), which were not thought to impact on recommendations and did not require footnotes in the guideline. No additional drug safety updates have been identified.

2018 surveillance summary

PPI dosing strategies

A systematic review (33) assessed PPIs, histamine 2 receptor antagonists, and prostaglandins in a range of indications. These drug classes were considered together as 'gastroprotectant drugs'. Overall, 849 trials were included, 580 of which assessed prevention of ulcers; 233 assessed healing; and 36 assessed treatment of acute upper gastrointestinal bleeding. The median duration of treatment was 1.4 months. Gastroprotectant drugs reduced rebleeding, need for blood transfusion, further endoscopic intervention, and surgery. There was no significant effect on mortality. PPIs had larger effects on further bleeding and blood transfusion than histamine 2 receptor antagonists.

Intravenous bolus or intravenous infusion

One network meta-analysis (34) of 39 studies assessed intravenous infusion compared with bolus delivery and with oral administration of PPIs. The number of participants was not reported in the abstract. It found no differences between infusion and bolus for mortality, length of stay in hospital, or risk of rebleeding at 72 hours, 1 week and 1 month or surgery. Oral PPIs were as effective as both intravenous bolus and intravenous infusion when considering length of stay in hospital and units of blood transfused. Oral PPIs were associated with lower need for surgery than intravenous infusion.

Two older systematic reviews (35,36) covering PPI dosing strategies were identified. Both studies found no significant differences between oral and intravenous administration of PPIs for any outcomes.

A randomised controlled trial (37) assessing bolus compared with infusion pantoprazole (n=113) found no differences in any outcomes. The dosing strategies were 80 mg bolus followed by 8 mg per hour infusion or 40 mg bolus twice daily.

High-dose or low dose

A systematic review (38) of 10 studies assessed high-dose compared with low-dose PPIs (n=1,651). All high-dose PPIs were delivered intravenously, low-dose PPIs were delivered intravenously, except in two studies that used oral PPIs. People on low-dose PPIs had fewer rebleeds than those on high doses. There were no significant differences in mortality or need for surgery. Additionally, no difference in mortality was seen when comparing use of pantoprazole with lansoprazole.

A post-hoc analysis of a randomised controlled trial (39) assessed the risks of rebleeding in people with Forrest oozing peptic ulcers compared with other stigmata. The overall trial assessed high-dose intravenous esomeprazole compared with placebo. The number of participants was not reported in the abstract. Forrest oozing peptic ulcers were associated with lower rebleeding rates than spurting arterial bleeds, adherent clots, and non-bleeding visible vessels.

Intelligence gathering

No additional intelligence relevant to this section was identified.

Impact statement

Evidence suggests little difference between oral and intravenous administration of PPIs for non-variceal upper gastrointestinal bleeds. There also appears to be little difference between administration by intravenous infusion and intravenous injection. Additionally, one systematic review suggests that high-doses of PPIs may increase rebleeding.

Current recommendations suggest using PPIs in people with confirmed non-variceal bleeding, but make no recommendations on routes of administration or dosage. The evidence-base does not indicate that an update is necessary at this time.

Although specific stigmata (Forrest oozing) of peptic ulcers may indicate lower risk of rebleeding than other stigmata, the evidence does not provide information on the difference in risk compared with no stigmata, or whether there was a beneficial effect of esomeprazole in this group.

This study is thus insufficient to impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Treatment after first or failed endoscopic treatment

1.4.5 Consider a repeat endoscopy, with treatment as appropriate, for all patients at high risk of re-bleeding, particularly if there is doubt about adequate haemostasis at the first endoscopy.

1.4.6 Offer a repeat endoscopy to patients who re-bleed with a view to further endoscopic treatment or emergency surgery.

1.4.7 Offer interventional radiology to unstable patients who re-bleed after endoscopic treatment. Refer urgently for surgery if interventional radiology is not promptly available.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

In previous surveillance in 2016, 2 meta-analyses (40,41) suggested that in people who had endoscopic therapy failure, surgery was more effective than arterial embolisation. However, the evidence from the meta-analyses was considered to be limited and further evidence to assess the effect on the guideline recommendations was indicated to be necessary.

2018 surveillance summary

Over the scope clips

A randomised controlled trial (42) assessed 'over the scope' clips compared with standard treatment in people with severe recurrent upper gastrointestinal bleeding (n=66). Standard therapy was 'through the scope' clips or thermal therapy plus adrenaline injection. Patients who had further bleeding could cross over to the 'over the scope' treatment because standard therapy had failed. Both recurrent and persistent bleeding occurred in fewer people treated with the 'over the scope' clip. No differences in rates of surgery or mortality were seen.

Angiographic embolisation

A randomised controlled trial (43) assessed angiographic embolisation compared with endoscopic therapy in people with bleeding peptic ulcers (n=241). There was no difference between groups in 30-day rebleeding, mortality, or death.

Second endoscopy

A randomised controlled trial (44) assessed scheduled second endoscopy after 24 to 36 hours in people with endoscopically confirmed bleeding peptic ulcer with stigmata who received initial endoscopic

therapy (n=319). Initial endoscopic therapy was clipping, thermal coagulation, or adrenaline. The control was not reported clearly in the abstract. There was no significant difference in rates of rebleeding, surgical or radiological intervention, duration of hospital stay transfusions or mortality.

Intelligence gathering

In previous surveillance in 2016, as well as in current surveillance, topic experts suggested a review of topical haemostatic agents, particularly Hemospray, in non-variceal bleeding. In previous surveillance, no suitable evidence was identified. One study of Hemospray in variceal bleeding was identified (see management of oesophageal varices below). Overall, there is insufficient evidence to suggest an update is needed in this area.

Impact statement

New evidence suggests that 'over the scope clips' may be more effective than standard 'through the scope clips. However, the results are likely to need to be confirmed in a larger study, particularly because of crossovers to the 'over the scope' group.

New evidence suggested that Hemospray may have benefits in treating acute upper gastrointestinal bleeding. Hemospray is delivered by endoscopy, so if it was used as in the trial, it would lead to an additional endoscopic procedure. Its role in UK practice is unclear because the study did not assess Hemospray compared with, or added to, other treatments delivered at endoscopy.

Several studies have shown embolisation to lack efficacy, including when compared with second endoscopy and with surgery. This intervention is not currently recommended, so there is no impact on the guideline.

One study suggested that scheduling second endoscopy in the absence of clinical need was not effective. No update in this area is necessary because this finding is consistent with the guideline's recommendations for second endoscopy according to patients' need.

New evidence is unlikely to change guideline recommendations.

Management of variceal bleeding

1.5.1 Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive haemostasis has been achieved, or after 5 days, unless there is another indication for its use*.

* At the time of publication (June 2012), terlipressin was indicated for the treatment of bleeding from oesophageal varices, with a maximum duration of treatment of 72 hours (3 days). Prescribers should consult the relevant summary of product characteristics. Informed consent for off-label use of terlipressin should be obtained and documented.

1.5.2 Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

In previous surveillance in 2016, a randomised controlled trial (45) (n=780) found no significant differences in rates of treatment success, control of bleeding, re-bleeding, or mortality between terlipressin, somatostatin, and octreotide when given before endoscopic treatment in people with acute variceal bleeding. A systematic review (46) also found no difference in rates of rebleeding between vasopressin, terlipressin, somatostatin and octreotide.

2018 surveillance summary

No relevant evidence on terlipressin was identified.

Intelligence gathering

A synthetic vasopressin (Agripressin) is available in the UK, which is licensed for control of bleeding from oesophageal varices. Somatostatin is not available in the UK.

Impact statement

In developing the guideline, the decision to recommend terlipressin was made based on evidence of effectiveness and a cost-effectiveness analysis. The guideline committee felt that terlipressin was more widely used than octreotide and that patients with variceal bleeds may benefit from terlipressin for co-existing indications such as hepatorenal syndrome.

Additionally, the guideline noted that vasopressin has significant side effects through constriction of coronary and peripheral vascular arteries. Terlipressin was noted to be used for control of variceal bleeding in clinical practice in the UK. Therefore, the additional evidence is unlikely to impact on the recommendations.

New evidence is unlikely to change guideline recommendations.

Oesophageal varices

1.5.3 Use band ligation in patients with upper gastrointestinal bleeding from oesophageal varices.

1.5.4 Consider transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from oesophageal varices is not controlled by band ligation.

Gastric varices

1.5.5 Offer endoscopic injection of *N*-butyl-2-cyanoacrylate to patients with upper gastrointestinal bleeding from gastric varices.

1.5.6 Offer TIPS if bleeding from gastric varices is not controlled by endoscopic injection of *N*-butyl-2-cyanoacrylate.

Previous surveillance

In 2016 surveillance, one randomised controlled trial (47) found no benefit of adding sclerotherapy to endoscopic ligation. Evidence from 2 systematic reviews (48,49) and one randomised controlled trial (50) suggested effectiveness of TIPS compared with endoscopic therapy. However, the results were mixed with regards to the key outcomes of mortality and rebleeding rates.

In the 2014 Evidence Update, no relevant evidence was identified.

2018 surveillance summary

We found 22 studies looking at treatment of variceal bleeding. Interventions, comparators, outcomes and results varied. Table 2 below shows a summary of these results.

Intelligence gathering

In 2016 surveillance, a topic expert noted that TIPS would be inappropriate for people with bleeding due to left-sided portal hypertension, which generally presents as a lone varix. This specific indication was thought to be rare, so no changes were made. No new evidence in this area was identified in the 2016 surveillance review.

No additional feedback was identified at the 2018 surveillance review.

Impact statement

The evidence appears to be inconsistent across studies. In several studies, band ligation was beneficial for some outcomes but not others. Overall, the evidence indicates that band ligation is effective for oesophageal varices. Similarly, cyanoacrylate and TIPS appear to be effective for gastric varices.

These findings are consistent with current recommendations to offer band ligation as first-line treatment for oesophageal varices and to offer TIPS as second line treatment in both oesophageal and gastric varices.

Studies of other interventions also tended to show efficacy for some outcomes but not others. There was no strong indicator of a need to update recommendations in this section of the guideline.

New evidence is unlikely to change guideline recommendations.

Table 2 Summary of intervention studies for variceal bleeding

Study	Type	n	Intervention	Comparator	Outcome	Result
Treatment of oesophageal varices						
Zhou 2018 (51) Oesophageal	SR	689 (6 studies)	Band ligation	Drug treatment	Mortality	Lower with band ligation
					Mortality caused by bleeding, rebleeding, rebleeding from varices	No difference
Lin 2017 (52) Oesophageal	SR	–	Band ligation plus drug treatment	Drug treatment	Mortality, Bleeding-related mortality;	No difference
					Rebleeding; Variceal rebleeding	Lower with band ligation plus drug treatment
			Band ligation plus drug treatment	Band ligation	Mortality, Bleeding-related mortality; Variceal rebleeding	No difference
			Band ligation plus drug treatment	TIPS	Rebleeding	Lower with band ligation plus drug treatment
					Mortality	No difference
					Bleeding-related mortality; Variceal rebleeding	Lower with TIPS
Halabi 2016 (53) Oesophageal	SR	608 (9 studies)	TIPS	Endoscopic therapy	1-year mortality; 1-year variceal rebleeding	Lower with TIPS
					1-year hepatic encephalopathy	No difference
Ibrahim 2018 (54) Oesophageal	RCT	86	Hemospray then endoscopic therapy	Endoscopic therapy	Rescue endoscopy before scheduled endoscopy, mortality	Lower with Hemospray
Sheibani 2016 (55) Oesophageal	RCT	90	Band ligation then repeat band ligation after 1 week until eradication	Band ligation then repeat band ligation after 2 weeks until eradication	Variceal eradication at 4 weeks	Higher with band ligation repeated every week
					Number of endoscopies until eradication; rebleeding at 4 weeks and 8 weeks; mortality	No difference
					Time to variceal eradication	Lower with band ligation repeated every week.
Li 2017 (56) Oesophageal	SR	– (4 studies)	Argon plasma coagulation after band ligation	Band ligation	Variceal recurrence	Lower with argon plasma coagulation after band ligation
					Fever	Higher with argon plasma coagulation after band ligation

Study	Type	n	Intervention	Comparator	Outcome	Result
					Mortality; bleeding recurrence;	No difference
Kamal 2017 (57) Oesophageal	RCT	40	Argon plasma coagulation after band ligation	Band ligation	Variceal recurrence; second ligation	Lower with argon plasma coagulation after band ligation
Lee 2016 (58) Oesophageal	RCT	71	Prophylactic antibiotic for 3 days (ceftriaxone 500 mg every 12 hours)	Prophylactic antibiotic for 7 days (ceftriaxone 500 mg every 12 hours)	Rebleeding, transfusion, 28-day mortality	No difference
Escorsell 2016 (59) Oesophageal	RCT	28	TIPS (after failed medical and endoscopic treatment)	Balloon tamponade (after failed medical and endoscopic treatment)	Treatment success; control of bleeding;	Higher with TIPS
					Transfusion, serious adverse events	Lower with TIPS
					6-week mortality	No difference
Treatment of gastric varices						
Zeng 2017 (60) Gastric	RCT	96	Lauromacrogol plus cyanoacrylate	Lipidiol plus cyanoacrylate	Rebleeding, treatment failure, complications	No difference
					Volume of cyanoacrylate delivered	Lower with lauromacrogol
Wang 2016 (61) Gastric	SR	– (5 studies)	BRTO	TIPS	Haemostasis; Technical success; Postoperative complications	No difference
					Postoperative bleeding; Postoperative encephalopathy	Lower with BRTO
Hassan 2018 (62) Gastric	RCT	60	Band ligation	Cyanoacrylate	Control of bleeding	Higher with band ligation
					Mortality	No difference
Treatment of both gastric and oesophageal varices						
Mansour 2017 (63) Gastric and oesophageal	RCT	120	Sclerotherapy plus band ligation	Band ligation	Number of sessions	Lower with sclerotherapy
					Rebleeding, variceal recurrence, adverse events	No difference
Chen 2016 (47) Gastric and oesophageal	RCT	96	Sclerotherapy plus band ligation; cyanoacrylate for gastric varices	Band ligation; cyanoacrylate for gastric varices	Rebleeding	Higher with sclerotherapy
					Mortality	No difference
Abstract did not specify type of varices						
	RCT	158			Rebleeding and death; rebleeding; serious adverse events	No difference

Study	Type	n	Intervention	Comparator	Outcome	Result
Abraldes 2016 (64) Unspecified			Simvastatin plus band ligation plus beta blocker	Placebo plus band ligation plus beta blocker	Death	Lower with simvastatin
					Death (Child C cirrhosis)	No difference
Wang 2017 (65) Unspecified	RCT	127	TIPS with 8 mm stent	TIPS with 10 mm stent	Hepatic encephalopathy	Lower with 8 mm stent
					Stent dysfunction, rebleeding, rebleeding plus no liver transplantation	No difference
Wang 2016 (66) Unspecified	RCT	258	TIPS with covered stent	TIPS with bare stent	Rebleeding; 4-year or 5-year mortality; refractory hydrothorax or ascites; restenosis; secondary intervention	Lower with covered stents
Lv 2017 (67) Unspecified	RCT	49	TIPS	Band ligation plus beta blocker	Rebleeding; restenosis	Lower with TIPS
					Mortality; hepatic encephalopathy; complications or adverse events	No difference
Qi 2016 (68) Unspecified	SR	– (3 studies)	TIPS	Drug treatment plus endoscopic therapy	Patients switched to TIPS (failure of first line therapy)	16–25%
					Overal survival; hepatic enchephalopathy	No difference
					Variceal rebleeding	Lower with TIPS
Albillos 2017 (69) Unspecified	IPD	389 (3 studies)	Band ligation plus beta blockers	Beta blockers	Rebleeding (people with Child A cirrhosis)	Lower with band ligation plus beta blockers
					Rebleeding (people with Child B or C cirrhosis)	No difference
		416 (4 studies)	Band ligation plus beta blockers	Band ligation	Rebleeding (all cirrhosis categories); Mortality (Child B or C cirrhosis)	Lower with band ligation plus beta blockers
Zhang 2017 (70) Unspecified	SR	2,185 (24 studies)	TIPS	Endoscopic therapy	Mortality; postoperative encephalopathy (all cirrhosis categories and Child C supgroup)	No difference
					Variceal rebleeding; bleeding-related mortality	Lower with TIPS
					Mortality (people with Child C cirrhosis)	Lower with TIPS
Tian 2018 (71) Unspecified	SR	1,540 (20 studies)	TIPS	Sclerotherapy	Rebleeding	Lower with TIPS
					Hepatic encephalopathy; length of stay in hospital	Higher with TIPS

Study	Type	n	Intervention	Comparator	Outcome	Result

n=number of participants. BRTO=Balloon-occluded retrograde transvenous obliteration. TIPS= transjugular intrahepatic portosystemic shunt. RCT=randomised controlled trial. SR=systematic review. IPD= Individual patient data meta-analysis.
Where a study did not report the overall number of participants in the abstract this is shown by the dash symbol (–).

Control of bleeding and prevention of re-bleeding in patients on NSAIDs, aspirin or clopidogrel

1.6.1 Continue low-dose aspirin for secondary prevention of vascular events in patients with upper gastrointestinal bleeding in whom haemostasis has been achieved.

1.6.2 Stop other non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 [COX-2] inhibitors) during the acute phase in patients presenting with upper gastrointestinal bleeding.

1.6.3 Discuss the risks and benefits of continuing clopidogrel (or any other thienopyridine antiplatelet agents) in patients with upper gastrointestinal bleeding with the appropriate specialist (for example, a cardiologist or a stroke specialist) and with the patient.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

No relevant evidence was identified in previous surveillance in 2016, or in the 2014 Evidence Update.

2018 surveillance summary

Restarting oral anticoagulants

A systematic review (72) of 7 studies (n=5,685) assessed the benefits and risks of oral anticoagulant therapy in people who had a major bleeding event. No significant difference in risk of stroke was seen between people who restarted oral anticoagulants and those who did not. People who restarted oral anticoagulants had a lower risk of thromboembolism. Results were reported to be similar for people who had gastrointestinal bleeds and those who had intracranial bleeds. People who restarted oral anticoagulants had significantly higher risk of recurrent major bleeding but lower risk of all-cause mortality. Overall, restarting oral anticoagulants was associated with clinical benefit.

A retrospective modelling study (73) used data from 3 hospitals to evaluate the timing of restarting vitamin K antagonists after upper gastrointestinal bleeding (n=207). Participants restarted vitamin K antagonists a median of 1 week after the bleed (range 0.2 to 3.4 weeks). Restarting vitamin K antagonists was associated with a reduced risk of thromboembolism and of death, but increased risk of recurrent bleeding. The authors concluded that the optimum timing for restarting vitamin K antagonists may be 3–6 weeks after a gastrointestinal bleed. However, they noted that this decision should take into account the degree of thromboembolic risk and the patient's values and preferences.

Non-steroidal anti-inflammatory drugs

A randomised controlled trial (74) assessed celecoxib 100 mg twice a day compared with naproxen 500 mg twice a day in people who had upper gastrointestinal bleeding and were negative for *H pylori* infection (n=514). Participants had arthritis and 'cardiothrombotic' conditions and all received esomeprazole 20 mg daily and took aspirin 80 mg daily. Recurrent gastrointestinal bleeding occurred more often in people taking naproxen compared with those taking celecoxib.

Intelligence gathering

Topic expert feedback indicated that aspirin may be withheld for a few days after upper gastrointestinal bleeding in some services in the UK.

Topic expert feedback additionally suggested that this section of the guideline should be updated to include advice for treating patients taking non-vitamin K oral anticoagulants.

Impact statement

The guideline recommends discussing the risks and benefits of continuing clopidogrel (or any other thienopyridine antiplatelet agents) in patients with upper gastrointestinal bleeding with the appropriate specialist. The guideline assessed the antiplatelet agents aspirin and clopidogrel because their irreversible inhibition of platelets means that their action lasts for around 10 days after stopping treatment.

An MHRA drug safety update on clopidogrel and proton pump inhibitors notes that: 'Use of either omeprazole or esomeprazole with clopidogrel should be discouraged. The current evidence does not support extending this advice to other PPIs.' This is thought not to affect current recommendations because discussion of the risks and benefits of continued treatment should take account of drug safety updates.

In terms of non-vitamin K oral anticoagulants, although the guideline does not include recommendations on this class of drugs, NICE has published advice on reversal of the anticoagulant effect of dabigatran: idarucizumab (ESNM73). This summarises the evidence for use of idarucizumab, which is licensed for rapid reversal of dagibatran, for example for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.

Evidence suggests that the benefits of continuing oral anticoagulants after a major bleeding event, including upper gastrointestinal bleeds outweigh the risks of future bleeds. Therefore, updating recommendations to include advice on

anticoagulant use is not thought to be necessary at this time.

A further study suggests that restarting vitamin K antagonists 3 to 6 weeks after upper gastrointestinal bleeding may be optimum for balancing the benefits with the risk of further bleeds. However, this study did not report using the patient's INR to guide decision-making, which is an important factor when using vitamin K antagonists. The guideline does not include specific recommendations about restarting vitamin K antagonists. This study is unlikely to impact on the guideline at this time.

The guideline recommends stopping non-steroidal anti-inflammatory drugs in the acute phase of upper gastrointestinal bleeding. One study suggests the celecoxib may be associated with fewer recurrent gastrointestinal bleeds than naproxen. However, the abstract did not report the incidence of other adverse events. Therefore, this study is unlikely to impact on current recommendations. Additionally, it does not influence the current recommendation to stop these drugs in the acute phase after upper gastrointestinal bleeding.

New evidence is unlikely to change guideline recommendations.

Primary prophylaxis for acutely ill patients in critical care

1.7.1 Offer acid-suppression therapy (H_2-receptor antagonists or proton pump inhibitors) for primary prevention of upper gastrointestinal bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug.*

* As of August 2016, only the H_2-receptor antagonists ranitidine and cimetidine are licensed for prophylaxis of gastrointestinal bleeding in acutely ill patients. The proton pump inhibitors omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole are not licensed for prophylaxis of gastrointestinal bleeding in acutely ill patients. The use of proton pump inhibitors or H_2-receptor antagonists other than ranitidine and cimetidine for this indication would be off label.

1.7.2 Review the ongoing need for acid-suppression drugs for primary prevention of upper gastrointestinal bleeding in acutely ill patients when they recover or are discharged from critical care.

Surveillance decision

This section of the guideline should not be updated.

Previous surveillance

In previous surveillance in 2016, no new evidence was identified. In the 2014 Evidence Update, 4 studies were identified (75–78) suggesting lower gastrointestinal bleeding with PPIs compared with H_2 receptor antagonists, and for prophylaxis

with either type of drug compared with placebo. No effects were seen on other outcomes.

2018 surveillance summary

We identified 9 studies assessing pharmacological treatments for stress ulcer prophylaxis. Table 3 below summarises the results of these studies. Overall, PPIs, histamine 2 receptor antagonists, and sucralfate appear to reduce gastrointestinal bleeding. There is little evidence to establish a definitive link between stress-ulcer prophylaxis and possible adverse events, particularly increases in pneumonia or *Clostridium difficile* infections.

One study (79) added naloxone to PPI prophylaxis for people with respiratory failure. Naloxone appeared to improve respiratory and gastrointestinal outcomes. Naloxone does not have a marketing authorisation for this indication in the UK.

Intelligence gathering

In 2016, the footnote to recommendation 1.7.1 was added to note that two histamine 2 receptor antagonists are licensed for stress ulcer prophylaxis, but no PPIs have such a license, which remains the case.

The 2016 surveillance also identified an ongoing study (the Stress Ulcer Prophylaxis in the Intensive Care Unit [SUP-ICU] trial; n=3,350). This study assessing stress-ulcer prophylaxis with pantoprazole compared with placebo has now completed, although results have not yet published.

Impact statement

Although many new studies of acid suppressing drugs for stress ulcer prophylaxis were identified, they generally support current recommendations. One study of naloxone suggests it may be beneficial for stress ulcer prophylaxis in people with respiratory failure. However, replication of these results in a larger study would be needed before they would impact on the current recommendations.

We will check regularly for publication of results from the SUP-ICU trial. We will then consider any impact of the results on recommendations.

New evidence is unlikely to change guideline recommendations.

Table 3: Summary of studies of stress ulcer prophylaxis

Study	Type	n	Intervention	Comparator	Outcome	Result
Alshamsi 2016 (22)	SR	2,117 (19 studies)	Proton pump inhibitors	H_2 receptor antagonists	Clinically important gastrointestinal bleeding; overt gastrointestinal bleeding	Lower with proton pump inhibitors
					Pneumonia, mortality; length of stay in intensive care unit	No difference

Study	Type	n	Intervention	Comparator	Outcome	Result
					Clostridium difficile infection	Not reported in the included studies
Alhazzani 2018 (80)	SR	7,293 (57 studies)	Proton pump inhibitors	H_2 receptor antagonists or sucralfate or placebo	Clinically important gastrointestinal bleeding	Lower with proton pump inhibitors
					Pneumonia	Probably higher with proton pump inhibitors
					Clostridium difficile infection	Reported in 1 study, but result not reported in the abstract
Toews 2018 (81)	SR	– (121 studies)	Any prophylaxis	No prophylaxis or placebo	Upper gastrointestinal bleeding	Lower with any prophylaxis
		2,149 (24 studies)	H_2 receptor antagonists	No prophylaxis or placebo	Upper gastrointestinal bleeding	Lower with H_2 receptor antagonists
		774 (8 studies)	Antacids	No prophylaxis or placebo	Upper gastrointestinal bleeding	Lower with antacids
		598 (7 studies)	Sucralfate	No prophylaxis or placebo	Upper gastrointestinal bleeding	Lower with sucralfate
		–	Proton pump inhibitors	No prophylaxis or placebo	Upper gastrointestinal bleeding	No difference (but data not reported in abstract)
		1,636 (18 studies)	Proton pump inhibitors	H_2 receptor antagonists	Upper gastrointestinal bleeding	Lower with proton pump inhibitors
		945 (8 studies); 450 (4 studies)	H_2 receptor antagonists; sucralfate	No prophylaxis or placebo	Pneumonia	No difference
		1,256 (10 studies)	Proton pump inhibitors	H_2 receptor antagonists	Pneumonia	No difference
Alquraini 2017 (82)	SR	3,121 (21 studies)	Sucralfate	H_2 receptor antagonists	Clinically important gastrointestinal bleeding, mortality; length of stay in intensive care unit	No difference
					Pneumonia	Lower with sucralfate
Lin 2016 (83)	RCT	120	Lansoprazole 30 mg	No prophylaxis	Apparent upper gastrointestinal bleeding	Lower with lansoprazole
					Ventilator-associated pneumonia; 30-day mortality	No difference
	RCT	214	Pantoprazole	Placebo	Clinically significant gastrointestinal bleeding	No cases in either group

Study	Type	n	Intervention	Comparator	Outcome	Result
Selvanderan 2016 (84)					*Clostridium difficile* infection	One case in pantoprazole group, no cases in placebo group
					Mortality; overt bleeding; daily haemoglobin concentration	No difference
Patients with respiratory failure						
He 2017 (79)	RCT	120	Naloxone plus pantoprazole	Pantoprazole	Partial pressure of oxygen; Partial pressure of carbon dioxide	Improved with naloxone
					Gastrointestinal bleeding and discomfort; discharge rate, intubation rate, mortality, length of stay	Lower with naloxone
Patients on enteral feeding						
Huang 2018 (85)	SR	889 (7 studies)	'Pharmacologic' stress ulcers prophylaxis	Placebo or no prophylaxis	Gastrointestinal bleeding; mortality; *Clostridium difficile* infection; length of stay in intensive care unit; duration of mechanical ventilation	No difference
					Pneumonia	Higher with stress ulcer prophylaxis
Yao 2017 (86)	RCT	52	Omeprazole plus early enteral feeding	Early enteral feeding	Mortality; stress ulcer incidence; faecal occult blood; gastric occult blood	Lower with omeprazole
					Nocturnal gastric pH; 24 hour gastric pH	Higher with omeprazole
					Insomnia, headache, abnormal liver function	No difference

SR=Systematic review, RCT=randomised controlled trial.

The symbol – represents missing data, most often the number of participants in a systematic review.

Information and support for patients and carers

1.8.1 Establish good communication between clinical staff and patients and their family and carers at the time of presentation, throughout their time in hospital and following discharge. This should include:

- giving verbal information that is recorded in medical records
- different members of clinical teams providing consistent information
- providing written information where appropriate

- ensuring patients and their families and carers receive consistent information.

Surveillance decision

No new information was identified at any surveillance review.

Research recommendations

No research recommendations were made for this guideline.

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