Surveillance report 2016 – Acute upper gastrointestinal bleeding (2012) NICE guideline CG141

Surveillance report
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Surveillance decision

We will not update the guideline at this time.

We will amend the guideline to include a footnote to recommendation 1.7.1 for acid-suppression therapy for primary prevention of upper gastrointestinal bleeding in acutely ill patients. This footnote is to make reference to the licensing limitations of H2-receptor antagonists and proton pump inhibitors for this indication.

Reason for the decision

We found 18 new studies through surveillance of this guideline.

This included new evidence on risk assessment, resuscitation and initial management, management of variceal and non-variceal bleeding and primary prophylaxis for acutely ill patients in critical care. This new evidence was considered to support current recommendations.

We did not find any new evidence on timing of endoscopy, control of bleeding and prevention of re-bleeding in patients on NSAIDs, aspirin or clopidogrel, or information and support for patients and carers.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

The surveillance identified the licensing limitations of H2-receptor antagonists and proton pump inhibitors for prophylaxis of gastrointestinal bleeding in acutely ill patients. Only the H2-receptor antagonists ranitidine and cimetidine are licensed for this indication. 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 H2-receptor antagonists other than ranitidine and cimetidine for this indication would be off-label.

Additionally, we identified relevant ongoing research that is expected to publish results in the next 3–5 years. The haemorrhage alleviation with tranexamic acid – intestinal system (HALT-IT) trial is assessing the effects of tranexamic acid on mortality, morbidity, blood transfusion, surgical intervention and health status in people with acute gastrointestinal bleeding. In addition, a trial comparing stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial) will consider mortality rates in people at risk of gastrointestinal bleeding.
Both trials have planned recruitment completion dates in 2017 and will be considered once results publish.

Other clinical areas

We also found new evidence in areas not covered by the original guideline that was not thought to have an effect on current recommendations. This evidence related to erythromycin for improved endoscopic imaging and tranexamic acid to manage upper gastrointestinal bleeding. However, there is a lack of consistent evidence for erythromycin and tranexamic acid to impact on the guideline at this time.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the new evidence, consultation with stakeholders and views of topic experts, we decided that an update is not necessary for this guideline.

See how we made the decision for further information.
Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

**Management of variceal bleeding**

We selected the systematic review and meta-analysis by Wang et al. (2015) for a full commentary. The evidence comparing pharmacological interventions to manage variceal bleeding was of low quality when assessed during the development of NICE guideline CG141. The evidence was also considered to be limited as many studies were conducted before the use of current endoscopic interventions. Data from the Wang et al. (2015) study may provide more evidence for the use of the different pharmacological interventions. The direct comparison of different vasoactive medications has the potential to inform decision-making when choosing between these drugs.

**What the guideline recommends**

NICE guideline CG141 recommends terlipressin for the initial treatment of patients with suspected variceal bleeding. Treatment should be stopped after definitive haemostasis has been achieved, or after 5 days, unless there is another indication for its use. The recommendation also notes that terlipressin treatment is indicated for bleeding from oesophageal varices and for maximum treatment duration of 72 hours. However, NICE guideline CG141 makes the recommendation outside the drug's indication based on the available evidence and advises that informed consent for off-label use be obtained and documented.

**Methods**

The Wang et al. (2015) systematic review and meta-analysis compared the effectiveness of vasoactive medications in people with oesophageal varices. A literature search identified randomised controlled trials that reported rates of re-bleeding following treatment with vasopressin, terlipressin, somatostatin or octreotide.

Inclusion criteria consisted of:

- randomised controlled trials
- population with oesophageal varices or oesophageal and gastric varices
- varices confirmed by endoscopy
- population treated with vasopressin, terlipressin, somatostatin or octreotide

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rates of re-bleeding reported.

Exclusion criteria consisted of:

- study design other than randomised controlled trial
- population with only gastric varices
- studies which included patients treated with endoscopic therapy for oesophageal varices over the previous month.

The meta-analysis presented the primary outcome of re-bleeding rates within 5 days and after 5 days following treatment. This outcome was derived from the inclusion of 6 randomised controlled trials combining a total of 1,224 patients. Data were analysed to compare vasopressin or terlipressin treatment with somatostatin or octreotide treatment.

Results

The rate of re-bleeding within 5 days of treatment was reported in 5 of the 6 studies and failed to find a significant difference between vasopressin or terlipressin treatment and somatostatin or octreotide treatment (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.51 to 1.50, Z statistic =−0.492, p=0.623).

The rate of re-bleeding after 5 days of treatment was reported in 2 of the 6 studies and failed to find a significant difference between vasopressin or terlipressin treatment and somatostatin or octreotide treatment (OR 1.12, 95% CI 0.64 to 1.95, Z statistic =0.399, p=0.690).

Strengths and limitations

Strengths

Methodologically this study contains clear and specific inclusion criteria that allowed identification of appropriate evidence. This was further enhanced with the use of quality assessment of the studies selected for inclusion.

The systematic review reported sufficient details of study characteristics and results from the included studies. The primary outcome of the study is an appropriate indicator of the efficacy of vasoactive medications and is of direct relevance to NICE guideline CG141.
Limitations

Although inclusion criteria are clearly defined, there is a lack of information on study restrictions and adherence to a protocol. The literature search was conducted in only 3 databases and studies were excluded if the full text was not available. These limitations could result in important and relevant studies being missed.

The studies included within the meta-analysis were prone to multiple sources of bias including lack of adequate randomisation and lack of blinding. The study's use of only the Delphi list as a quality assessment tool could be considered inadequate as it is designed to be used alongside another validated tool. These methodological limitations could also affect the reliability of the results.

The study only considered re-bleeding as the primary outcome and would have benefited from analyses of mortality, further interventions, length of hospital stay and adverse events. The inclusion of additional outcomes would have increased the relevance to NICE guideline CG141.

Only 3 of the included studies provided information on the endoscopic treatment used. Current clinical practice advocates the use of vasoactive medications in conjunction with endoscopic treatment. The inclusion of studies where vasoactive medication was potentially used in isolation could limit the generalisability of the results to current practice.

The study population matches NICE guideline CG141 for people with oesophageal varices however the guideline review question also covers people with gastric varices. The exclusion of people with only gastric varices from the study limits the generalisability of the results to a partial population in NICE guideline CG141.

The inclusion of somatostatin as an intervention in this study may have limited applicability to NICE guideline CG141. Currently, the somatostatin analogues lanreotide and pasireotide are not licensed for treatment of bleeding oesophageal varices. The study does not indicate which of the somatostatin analogues were used in the included studies.

The authors also note a number of limitations of the systematic review and meta-analysis:

- Variations in the dose and duration regimens of medications across the included studies limit the comparability of treatments.

- The primary outcome was not the main endpoint in the included studies, which may have been a contributing factor to the small sample size.
A confounding factor was that initial treatment with different endoscopic therapies was not considered and may have affected the results given the associated bleeding risks of these treatments.

An adequate sensitivity analysis and an analysis of publication bias could not be conducted due to the low number of included studies.

Impact on guideline

The results of the study would suggest comparable efficacy between pharmacological treatments for oesophageal varices after initial treatment. The NICE guideline CG141 recommendation to offer terlipressin was made based on favourable health economic evidence and the availability of evidence for the important primary outcomes. The results of the Wang et al. (2015) study are inconsistent with the current recommendation in NICE guideline CG141 to offer terlipressin for suspected variceal bleeding at presentation. However, the restricted search strategy could have resulted in relevant studies being missed. In addition, the low quality of the included studies could have affected the reliability of the results. Generalisability to NICE guideline CG141 is limited by the inclusion of only 1 primary outcome in the analysis, a population focused towards oesophageal varices and inclusion of studies without current clinical practice. Given the limitations of this study, the results are unlikely to impact on recommendations in NICE guideline CG141.

Management of variceal bleeding – gastric varices

We selected the meta-analysis by Qi et al. (2015) for a full commentary because results of this study potentially challenge the current recommendation in NICE guideline CG141 and suggest improved efficacy of transjugular intrahepatic portosystemic shunt (TIPS) compared with medical or endoscopic therapy.

What the guideline recommends

For management of upper gastrointestinal bleeding from gastric varices, NICE guideline CG141 recommends initial treatment with endoscopic injection of N-butyl-2-cyanoacrylate. If bleeding is not controlled with initial treatment, the recommendation is to offer treatment with TIPS.

Methods

The Qi et al. (2015) meta-analysis compared the effectiveness of TIPS to medical or endoscopic therapy in cirrhotic patients with acute variceal bleeding. The final analysis included 6 studies with a total 388 patients and considered both randomised and non-randomised comparative studies. For inclusion in the analysis, studies were required to include any of the following outcomes:
- Treatment failure to control acute bleeding and/or early re-bleeding.
- Rates of re-bleeding following treatment as identified at any stage of the study including during follow-up.
- Rates of overall survival consisting of the number of patients who survived during follow-up.
- Rates of bleeding-related death consisting of the number of patients with re-bleeding following treatment as the cause of death.
- Rates of post-treatment hepatic encephalopathy.

Additional inclusion criteria consisted of:

- Study populations of cirrhotic patients with acute oesophageal, gastric or mixed variceal bleeding.
- Studies where TIPS was the intervention.
- Studies where medical or endoscopic therapy was the comparator.

Results

The study included 3 randomised controlled trials and 3 non-randomised studies. All of the outcomes had a combination of randomised and non-randomised eligible studies. The populations in each study varied with oesophageal bleeding in 3 studies and gastric bleeding in 1 study. A mixed population of oesophageal and/or gastric bleeding was included in the other 2 studies.

The rate of treatment failure was reported in 5 of the total 6 studies and found a significant reduction for TIPS compared with medical or endoscopic therapy (OR 0.22, 95% CI 0.11 to 0.44, p<0.0001).

The rate of overall re-bleeding was reported in 5 of the total 6 studies and found no significant difference between TIPS and medical or endoscopic therapy (OR 0.27, 95% CI 0.06 to 1.29, p=0.10).

The rate of overall survival was reported in 6 studies and found a significant improvement for TIPS compared with medical or endoscopic therapy (hazard ratio [HR] 0.55, 95% CI 0.38 to 0.81, p=0.002).
The rate of bleeding-related death was reported in 4 of the total 6 studies and found a significant reduction for TIPS compared with medical or endoscopic therapy (OR 0.19, 95% CI 0.06 to 0.59, p=0.004).

The rate of post-treatment hepatic encephalopathy was reported in 5 of the total 6 studies and found no significant difference between TIPS and medical or endoscopic therapy (OR 1.37, 95% CI 0.63 to 2.99, p=0.43).

Strengths and limitations

Strengths

The study contained robust inclusion criteria that were clearly specified with definitions of the primary outcomes. Appropriate restrictions were applied to the literature search to ensure a broad range of potentially included studies. A quality assessment was conducted of the studies selected for inclusion. The meta-analysis included heterogeneity and sensitivity analyses. The study also included a range of primary outcomes that are directly relevant to NICE guideline CG141.

Limitations

The population in the study consists of patients with liver cirrhosis, primarily oesophageal varices and mostly deemed 'high risk'. The population within the included studies is not specific to people with gastric varices. Although these are all sub-groups in NICE guideline CG141, the results may not be fully generalisable to people with acute upper gastrointestinal bleeding from gastric varices as indicated in the review question.

Although TIPS is a recommended treatment, it was not investigated whether it is more effective as an initial or secondary treatment. Data on the timing of TIPS treatment would have directly addressed the review question in NICE guideline CG141.

Only 3 randomised controlled trials were included in the final selection of studies and were all deemed low quality. The authors also highlighted the relatively small sample size and inclusion of non-randomised studies. The outcomes all had a combination of randomised and non-randomised eligible studies which may impact on the reliability of the results. Further potential bias was identified by the inclusion of 2 studies from the same research group and 1 study with an inadequate follow-up period to ascertain reliable mortality data.
Impact on guideline

The results support the use of TIPS for variceal bleeding with benefit over medical or endoscopic therapy. However, the population in the study primarily consists of a narrow group of patients with liver cirrhosis, oesophageal varices and deemed 'high risk'. The results do not provide any data on the timing of TIPS intervention and whether it is more effective as an initial treatment or to be used following alternative treatments. The evidence is unlikely to affect the recommendation to offer TIPS if gastric variceal bleeding is not controlled by medical or endoscopic therapy.
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of acute upper gastrointestinal bleeding (2012) NICE guideline CG141.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 9 new studies in a search for randomised controlled trials and systematic reviews published between 20 February 2014 and 6 April 2016.

Evidence from 9 studies identified in an evidence update published 2 years after publication of the guideline was also considered.

From all sources, 18 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: summary of new evidence from surveillance and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline. Overall, three stakeholders commented. See appendix B for stakeholders' comments and our responses.
Three stakeholders commented on the proposal to not update the guideline and all 3 agreed with the decision. Stakeholders also highlighted for future surveillance the ongoing HALT-IT trial on tranexamic acid. This study will be monitored in the surveillance trial tracker and considered when results become available.

Overall, we decided not to update the guideline.

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

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