Management of bleeding gastroduodenal ulcers

Stig Borbjerg Laursen, Henrik Stig Jørgensen & Ove B. Schaffalitzky de Muckadell

The guideline has been approved by the Society of Danish Society for Gastroenterology and Hepatology September 4, 2011

Correspondence: Ove B Schaffalitzky de Muckadell, Department of Gastroenterology S, Odense University Hospital, DK-5000, Odense C, Denmark
E-mail: Sdm@OUH.regionsyddanmark.dk

Dan Med J 2012;59(7):C4473

Abstract

Description: A multidisciplinary group of Danish experts developed this guideline on management of bleeding gastroduodenal ulcers. Sources of data included published studies up to March 2011. Quality of evidence and strength of recommendations have been graded. The guideline was approved by the Danish Society of Gastroenterology and Hepatology September 4, 2011.

Recommendations: Recommendations emphasize the importance of early and efficient resuscitation. Endoscopy should generally be performed within 24 hours, reducing operation rate, rebleeding rate and duration of in-patient stay. When serious ulcer bleeding is suspected and blood found in gastric aspirate, endoscopy within 12 hours will result in faster discharge and reduced need for transfusions. Endoscopic hemostasis remains indicated for high-risk lesions. Clips, thermocoagulation, and epinephrine injection are effective in achieving endoscopic hemostasis. Use of endoscopic monotherapy with epinephrine injection is not recommended. Intravenous high-dose proton pump inhibitor (PPI) therapy for 72 hours after successful endoscopic hemostasis is recommended as it decreases both rebleeding rate and mortality in patients with high-risk stigmata. Although selected patients can be discharged promptly after endoscopy, high-risk patients should be hospitalized for at least 3 days after endoscopic hemostasis. Patients with peptic ulcer bleeding who require secondary cardiovascular prophylaxis should start receiving acetylsalicylic acid (ASA) again as soon as cardiovascular risks outweigh gastrointestinal risks. Patients in need of continued treatment with ASA or a nonsteroidal anti-inflammatory drug should be put on prophylactic treatment with PPI at standard dosage. The combination of 75mg ASA and PPI should be preferred to monotherapy with clopidogrel in patients needing anti-platelet therapy on the basis of indications other than coronary stents

Introduction

This guideline is prepared on the basis of the report ”Final proposal for interdisciplinary national clinical guideline for bleeding gastroduodenal ulcers”[1] from the Danish National Indicator Project and has been approved by the Danish Society for Gastroenterology and Hepatology September 4, 2011.

Subject-area delimitation

The guideline deals with the treatment of patients bleeding from chronic peptic ulcerations located to the stomach and/or duodenum and provides recommendations based on best practice in the assessment and management of peptic ulcer bleeding of a severity that leads to admission to hospital.

Background

Bleeding gastroduodenal ulcers are frequent and are the cause of some 2000 admissions annually in Denmark. Despite the development of more potent acid-inhibiting drugs and improved endoscopic techniques, mortality has remained unchanged at about 10% for a great many years. This is presumably a consequence of increasing age and an increased frequency of competing illness in.

Definitions

Bleeding peptic ulcer is defined as the occurrence of haematemesis and/or melaena and/or an unexplained drop in B-haemoglobin in a patient in whom a subsequent endoscopy documents that the source of bleeding is a chronic peptic ulcer. *Chronic ulcerations* are defined as ulcers with a visible loss of substance that penetrate the

muscular layer of tunica mucosa and the proper mucous membrane; these ulcers should not be confused with acute erosions.

Review of included topics

1. Admission and circulatory restoration

Initial assessment and treatment of patients with suspected ulcer bleeding is based on the ABCDE principles: Airway, Breathing, Circulation, Disability and Exposure/Environment.[2] Staff should be competent in the recognition of airway problems, use of basic airway manoeuvres, and when to call upon staff trained in advanced airway therapy.

Unobstructed airways and sufficient respiration is secured. Peripheral oxygen saturation should be measured and be ≥ 93%. Oxygen (10-15L/min) should be administered to patients with haemodynamic disturbance in order to secure adequate delivery of oxygen and avoiding global hypoperfusion and tissue hypoxia.[3]

Treatment of circulatory insufficiency is the cornerstone of the initial management. A minimum of two large peripheral IV lines are established and kept open with isotonic NaCl. If the patient is haemodynamically unstable, 1,000-2,000 ml isotonic NaCl or Ringer acetate is rapidly infused to ensure tissue perfusion. A Cochrane review comparing crystalloid and colloid fluid restoration demonstrated no significant statistical difference,[4] and as colloids may interfere with haemostasis, crystalloids are recommended.

In accordance with the guidelines from the National Board of Health, Denmark,[5] balanced blood component therapy in the ratio:

Erythrocytes 3 : fresh frozen plasma 3 : platelets 1

is initiated in life threatening bleeding. 0 rhesus negative blood can be used until compatible blood becomes available. Platelets are administered from the beginning simultaneously with infusion of fresh frozen plasma and erythrocytes in separate IV lines. The need of volume replacement should be assessed by monitoring blood pressure, heart rate, peripheral perfusion and oxygen saturation.

Care should be taken to avoid overloading, especially i patients with heart failure, and in risk of development of pulmonary oedema.

In patients with circulatory distress, insertion of a gastric tube can be instrumental in establishing the cause of circulatory failure as a result of upper gastrointestinal bleeding. Conversely, clear gastric aspirate cannot rule out even severe bleeding and must not be used as an argument for postponing upper endoscopy. Gastric tube insertion should not be done as a matter of routine.

The following blood samples are to be taken initially: B-Haemoglobin, B-Platelets, INR, P-Na, P-K, P-Albumin, P-Creatinine, P-Urea, Blood-type, BAC test and ECG.

Prognostic factors from case histories include a description of the occurrence of coffee-ground coloured/red haematemesis, melaena/haematochezia and syncope in conjunction with the aforementioned symptoms. Intake of NSAID/ASA, other platelet-inhibiting drugs, vitamin K antagonists and SSRI is recorded. Details, or clinical suspicion, of co-morbidity (particularly heart, liver, kidney and pancreas) and previous aortic surgery are important for prognostic reasons, and also of significance for optimal resuscitation and evaluation of the possibility of varicose bleeding, aortoenteric fistula or pancreatic pseudocyst haemorrhage.

2. Monitoring

Patients with upper GI bleeding should be admitted, assessed and managed in a dedicated bleeding unit, which in a cohort study was shown to reduce mortality.[6]

Only a sparse number of studies are available on optimal observation in connection with ulcer bleeding, for which reason the recommendations below are based on consensus.[1]

The vital parameters: Heart rate, blood pressure, oxygen saturation, respiratory rate, diuresis and level of consciousness are monitored every 15 minutes until the patient has stabilized, then once an hour. Fluid balance should be documented on specific charts.

In conjunction with endoscopy the level of consciousness is observed continuously, as are respiratory rate, blood pressure, heart rate and oxygen saturation. Continuous ECG monitoring may be useful. Supplementary monitoring with invasive arterial/venous pressure measurements and hourly urinary output should be considered in patients in haemodynamic distress.

Following a haemostatic procedure, respiratory rate, heart rate, blood pressure, level of consciousness and oxygen saturation should be recorded at regular intervals with an eye to early identification of rebleeding. Until four hours after haemostasis is achieved, it is recommended checking parameters every half an hour, from 5-12 hours once an hour, from 13-24 hours every four hours and then a minimum of three times a day.

Rebleeding occurs in 14%[7] and must be suspected where haematemesis, fresh melaena/haematochezia, syncope,

arterial hypotension, tachycardia, falling B-Haemoglobin and lack of normalization of P-Urea is observed.

3. Timing of endoscopy

Patients with suspected ulcer bleeding should generally be endoscoped within 24 hours of being hospitalized, thereby reducing the need for surgical haemostasis, the rebleeding rate and in-patient stay.[8]

On suspicion of serious ulcer bleeding and occurrence of bloody gastric aspirate, endoscopy should be endeavoured within twelve hours. A randomized study has shown that this achieves earlier discharge and reduces the need for transfusion.[9]

Endoscopy within 6-8 hours generally entails an increased risk of poor overview conditions, greater risk of aspiration and an increased therapy rate, and no improvement of prognosis.[8]

If, circulatory stabilization, despite intensive resuscitation, is not possible, upper endoscopy should be performed immediately on vital indication.

4. Endoscopic treatment

4.1 Indication and purpose

Endoscopic treatment is indicated in Forrest I-IIb ulcers. In addition to primary haemostasis, endoscopic treatment of Forrest I-IIa ulcers will result in a lower rebleeding rate, rate of surgery and mortality.[10] Endoscopic treatment of ulcers with an adherent clot - i.e. coagulum that cannot be removed by vigorous irrigation or suction – is a subject of controversy.[11] A meta-analysis has shown that endoscopic treatment for this type of ulcer does reduce the rate of rebleeding and operation, but mortality remained unchanged.[12] However, the available studies are, as far as treatment is concerned, methodologically heterogeneous. The most frequently used treatment modality is injection therapy followed by removal of the clot and treatment of any underlying bleeding stigmata with a secondary treatment modality.

4.2 Modalities of therapy

4.2.1 Adrenaline-saline injection

In most instances, treatment with adrenaline-saline injection (1:10,000) is the technique of choice as the first modality, since the method is good for achieving haemostasis[13-16] and creating an overview of the source of bleeding. Three randomized studies have shown a clear correlation between the volume of adrenaline-saline injected and the rebleeding rate.[17-19] The rebleeding rate is halved if the injected volume is increased from 5-10 ml to 13-20 ml.[17] For the purpose of reducing the rebleeding rate, therefore, it is recommended always to inject a total volume of at least 10 ml adrenaline-saline, irrespective of already obtained haemostasis. Injecting a total volume greater than 30 ml increases the risk of developing protracted abdominal pains as well as perforation, and should therefore be avoided.[18]

4.2.2 Contact thermal probe

Treatment with contact thermal probes includes use of heater probe and multipolar electrocoagulation. Both types of thermal probes are effective.[20-22] The mechanism of action is coaptive coagulation. This is achieved by compression of the vessel with a steady pressure, and subsequent congealing by supplying heat.

4.2.3 Hemoclip

The aim of treatment with Hemoclips is to achieve mechanical haemostasis. Hemoclips are particularly well suited to a visible vessel. However, application of a hemoclip can be technically challenging, especially in retroflexion and in the case of ulcers located to the posterior wall of the duodenal bulb. The evidence for the effectiveness of hemoclips as compared with a thermal probe is scanty and in several cases contradictory.[23-25] Overall, the methods seem to be of equal value.[26]

4.2.4 Injection with sclerosing drugs

Injection of a sclerosing drug such as polydocanol (Aethoxysclerol) and ethanol used to be employed frequently to obtain haemostasis. However, due to reports on subsequent fatal necrotization[27-28] and the emergence of better alternatives, injection treatment with sclerosing drugs can no longer be recommended as the first choice.

4.2.5 Argon plasma coagulation

The evidence for efficacy of argon plasma coagulation in the treatment of ulcer bleeding is modest.[29-31] The effectiveness of this method is limited due to a modest depth effect and lack of coaptive coagulation. Treating ulcer bleeding with argon plasma coagulation cannot be recommended, therefore.

4.3 Mono versus dual therapy

There are numerous studies, including a number of meta-analyses, comparing different forms of endoscopic therapy. An important aspect in this regard is whether monotherapy with a particular form of therapy is associated with the same outcome as dual therapy. Unfortunately, there is divergence between the studies in several areas.

Use of adrenaline-saline injection as monotherapy is associated with a rebleeding rate of just under 20%.[32] A Cochrane analysis has shown that by adding a secondary treatment modality it is possible to reduce both rebleeding rate, the rate of surgery and mortality.[32] Adrenaline-saline injection should always be supplemented with a secondary form of therapy, therefore.

A meta-analysis from 2007 concluded that monotherapy with a thermal probe was as effective as combination ther-

apy with adrenaline.[33] The validity of this conclusion is questionable, however.[34-36] A subsequent meta-analysis from 2009 opted, in relation to the aforementioned meta-analysis, to exclude two studies.[37] The rationale behind this was that one study used injection of a placebo solution in the treatment arm with thermal monotherapy, which could have had a therapeutic effect. The second study was excluded because the probe used was unipolar. After excluding the aforementioned studies, the rebleeding rate was found to be lower with combination therapy. Treatment with a thermal probe should always be supplemented with a form of secondary therapy, therefore.

Only few studies are available comparing monotherapy with Hemoclips with combination therapy. In the meta-analyses described previously, monotherapy with Hemoclips is deemed to be on a par with combination therapy.[33,37]

5. Invasive procedures

5.1 Transcatheter arterial embolization

If endoscopic haemostasis cannot be achieved, the patient should have transcatheter arterial embolization (TAE) performed without delay. TAE and surgery are of equal efficacy in terms of rebleeding rate, need for further surgical intervention and mortality.[38] According to a recent retrospective study, TAE seems to be associated with a lower complication rate than surgical haemostasis.[39]

If no active bleeding can be identified by angiography in connection with embolization, "blind embolization" can be undertaken on the basis of knowledge of the ulcer's anatomical location.[40] A Hemoclip should be placed in the edge of the ulcer during the preceding endoscopy, thus facilitating identification of the bleeding vessel If attempts to access the bleeding arteries via the femoral arteries are unsuccessful access via brachial arteries can be used instead.

5.2 Surgical haemostasis

If endoscopic haemostasis cannot be achieved and TAE is not feasible, an emergency operation must be performed. It is recommended undertaking transfixion of the ulcer and the bleeding vessel with or without concurrent vagotomy rather than gastric resection. Mortality after both interventions is identical,[41-42] for which reason the most simple operation should be used. Access to gastric ulcers is most easily obtained through a transverse gastrotomy. With duodenal ulcers at the posterior wall of the duodenal bulb, the gastroduodenal artery is often involved. Here a longitudinal gastrotomy is performed in the anterior wall, sparing the pylorus wherever possible. The artery can then be transfixed above and below the bleeding site with a 2-0, 0 or 1 monofilament slowly absorbable suture. It is recommended to use a 5/8 27 mm round needle, as larger needles increases the risk of choledochal lesion.[43] Gastro and duodenotomies are closed in one layer, extramucosally or in all layers. A longitudinal incision through pylorus is always closed transversely. In Billroth II resectees it is sometimes not possible to suture or staple the duodenum distally to the ulcer. In that case the transfixed ulcer base is left in the posterior wall of the duodenal bulb, the anterior wall is sutured down to the anal part of the fibrous ulcer and a drain inserted into the duodenal lumen for decompression. The drain is best positioned via a separate incision laterally into another part of duodenum.[43] In general, extraluminal drains are not necessary after surgery for ulcer bleeding.

6. Rebleeding

At the first episode of rebleeding, therapeutic endoscopy is repeated if considered technically possible. Repeated endoscopic treatment is less effective than surgery with regard to achieving haemostasis, but equal in terms of survival and associated with fewer complications.[44] In the event of repeated rebleeding, treatment with re-endoscopy, TAE or operation must be considered on the basis of a case-by-case judgement and local expertise.

6. Medical treatment

6.1 Proton pump inhibitors (PPI)

A Cochrane analysis has shown that, overall, treatment with PPI reduces the rebleeding rate and the need for surgical haemostasis as compared with treatment with placebo or histamine-2 receptor antagonists.[45] For endoscopically treated ulcers with active bleeding or a visible vessel, it was found that infusing high-dose PPI (80mg bolus followed by 8mg/hour) in addition resulted in reduced mortality. Treatment with a lower dose of PPI (intravenous or oral) reduced the rebleeding rate, but *not* the mortality.[11] Direct comparison of intravenous versus oral treatment with PPI has only been investigated in a few studies, which generally bear the mark of insufficient power.[46-48] A Cochrane analysis has shown that treatment with PPI prior to endoscopy reduces the proportion of patients in whom endoscopic treatment is indicated.. However, this is followed neither by a lower rebleeding rate, rate of surgery nor mortality.[49] Furthermore treatment with PPI impedes the diagnosis of Helicobacter pylori infection. Treatment with PPI prior to endoscopy cannot be recommended and must not delay the timing of upper endoscopy.

All patients with ulcer bleeding should be placed on treatment with proton pump inhibitors. Low-risk ulcers (Forrest IIc-III) are treated with oral PPI at a dose equipotent to 20 mg omeprazole daily. In the case of ulcers requiring endoscopic treatment, high-dose infusion treatment for three days is recommended before switching to oral treatment. Treatment equipotent to 80 mg omeprazole as bolus followed by 8 mg/hour for 72 hours is recommended.

6.2 Pausing treatment with ASA, clopidogrel, AK, NSAID and SSRI

When discontinuing well-indicated ASA treatment, the risk of developing arterial thrombosis is almost doubled.[50] Premature withdrawal of anti-platelet therapy is thus the most significant risk factor for stent thrombosis among patients with coronary stents. Patients developing ulcer bleeding on low-dose ASA treatment and receiving high-dose intravenous PPI after endoscopic treatment have lower mortality, but no statistically significant increase in rebleeding rate, assuming continued low-dose ASA treatment.[51] The platelet function in normal subjects is inhibited for up to five days after withdrawal of clopidogrel or aspirin, but presumably for a shorter time in bleeding patients. Consequently, both drugs can be paused for 24 hours until the bleeding has stopped and the situation is stabilized.

It is recommended pausing ASA, clopidogrel, AK, NSAID and SSRI in the presence of ulcer bleeding. Low-dose ASA can be resumed after 24 hours if there is no sign of bleeding in progress and high-dose IV PPI is given. Treatment with clopidogrel or other thienopyridines in patients with coronary stents can be resumed after three days. In case of doubt it is recommended to consult a cardiologist. Unnecessary NSAID intake should be discontinued. Treatment with AK and SSRI can be resumed after five days.

6.3 Tranexamic acid

A systematic view and meta-analysis has found that treatment with tranexamic acid can possibly reduce mortality, but the included studies were characterized by heterogenicity, inclusion of bleeding sources other than ulcer disease and inconsistent endoscopic therapy.[52] Furthermore rebleeding and need of surgical treatment was not reduced. Therefore, there is insufficient evidence to recommend the use of tranexamic acid for ulcer bleeding.

6.4 Thrombosis prophylaxis

Deep vein thrombosis (DVT) is a frequent complication following abdominal surgery (7-45%).[53] A Cochrane analysis has shown that extended treatment with low-molecular heparins (LMH) following major abdominal operations reduces the risk of developing venous thromboembolism without increasing the risk of postoperative bleeding.[54] Supplementary mechanical treatment with graduated compression stockings and early mobilization further reduces the occurrence of thromboembolic events.[55]

Following surgery for bleeding ulcer patients should be treated with LMH and compression stockings postoperatively. The treatment can beneficially be continued for four weeks.

7. Nutrition

There are few data only on the importance of nutrition for ulcer bleeding. A randomized study found that resuming oral intake one to two days after endoscopic therapy reduced in-patient stay without affecting the outcome.[56]

It is recommended that patients with endoscopic/endovascular/surgically treated bleeding ulcer disease are allowed oral intake of clear liquids for the first 24 hours after the procedure and then a normal diet. Patients with low-risk ulcer disease (Forrest IIc-III) without clinical suspicion of significant bleeding can be given a normal diet once the effect of the pharyngeal analgesia has worn off.

8. Discharge

Several studies have shown that patients at low risk of rebleeding or mortality can be discharged early on the course.[57-59] Thus patients with low-risk ulcers (Forrest IIc-III) without circulatory distress, or serious competing illness, can often be discharged within 24 hours of endoscopy. Following endoscopy, the Rockall score can be used to select low-risk patients.[59]

Among patients requiring endoscopic treatment who rebleed within a month, the majority (60-76%) rebleed within 72 hours.[60-62] It is therefore recommended not to discharge patients requiring endoscopic treatment for bleeding peptic ulcer earlier than after 72 hours' PPI infusion.

9. Aftercare

9.1 Helicobacter pylori infection

All patients with ulcer disease must have the Helicobacter pylori status established and helicobacter-positive patients should receive eradication therapy in order to reduce the recurrence rate.[63] Reference is made to the DSGH guideline on the diagnosis and treatment of Helicobacter pylori infection.

9.2 Monitoring gastric ulcers

If a satisfactory number of biopsies (5-7) has not been taken from patients with gastric ulcers or the experienced endoscopist is in doubt the possibility of malignancy, follow-up gastroscopy must be performed after 6-8 weeks.[64]

9.3 PPI prophylaxis

ASA/NSAID intake is associated with an increased relative risk of ulcer complication of 4-7.[65] During ASA treatment, recurrence of ulcer bleeding is prevented just as effectively with omeprazole 20 mg and HP eradication, while only PPI prevents recurrence of ulcer bleeding on NSAID treatment.[66] In patients with previous ulcer bleeding, long-term treatment with clopidogrel 75 mg produces 8 times more bleeding recurrences than the combination of ASA 80-100 mg and PPI.[67,68] A combination of PPI and ASA

seems safer in terms of bleeding than a combination of PPI and clopidogrel.[69] It is controversial whether pantoprazole should be preferred to other types of PPI in patients being treated with clopidogrel.[70] The significance of any PPI-clopidogrel interaction is not clarified.

It is recommended that patients with a need for continued ASA or NSAID treatment are given prophylactic treatment with PPI at standard dosage. The combination of 75 mg ASA and PPI should be given preference over monotherapy with clopidogrel in patients needing platelet-inhibiting treatment on the basis of indications other than coronary stents.

Levels of evidence for clinical recommendations

Admission and circulatory restoration	
Immediate and intensive circulatory stabilization is vital to survival	**Evidence II**
Resuscitation with infusion of colloids is no more effective than crystalloids, for which reason the latter should be preferred	**Evidence Ia**
In the event of circulatory failure, balanced blood component therapy should be initiated as quickly as possible	**Evidence IV**
In patients with circulatory failure highest possible oxygen supplement should be initiated	**Evidence IV**
Insertion of a nasogastric tube should not be done routinely	**Evidence IV**
Monitoring	
Patients with upper gastrointestinal bleeding should be managed in a dedicated unit with specially trained staff, thereby reducing mortality	**Evidence II**
Documentation of administration of fluids and blood on dedicated charts	**Evidence IV**
Time intervals for observation following admission, endoscopy and surgery	**Evidence IV**
Timing of endoscopy	
Endoscopy should generally be performed within 24 hours, reducing operation rate, rebleeding rate and duration of in-patient stay	**Evidence II**
When serious ulcer bleeding is suspected and blood found in gastric aspirate, endoscopy within 12 hours will result in faster discharge and reduced need for transfusions	**Evidence IV**
In general, endoscopy within 6-8 hours entails an increased risk of poor visibility due to retained blood, greater risk of aspiration and an increased rate of therapy that will not improve the prognosis.	
Endoscopic treatment	
Endoscopic treatment is indicated for Forrest Type I-IIb ulcers	**Evidence Ia**
Initial treatment with injection of 10-25 ml adrenaline-saline is efficient in achieving haemostasis and reducing rebleeding rate	**Evidence Ib**
Monotherapy with adrenaline-saline injection or heater probe should be avoided	**Evidence Ia**
Monotherapy with Hemoclip is just as effective as combination therapy	**Evidence Ia**
Secondary treatment with heater probe and Hemoclip is of equal value	**Evidence Ia**
Invasive procedures	
TAE and surgery are equal in terms of rebleeding rate and mortality	**Evidence II**
TAE is considered to be associated with a lower complication rate than surgical haemostasis	**Evidence IV**
In the case of surgical haemostasis, transfixion of the ulcer is preferred	**Evidence II**
Rebleeding	
First rebleeding episode should, if technically possible be treated endoscopically	**Evidence Ib**
Pharmacological treatment	
Treatment with PPI following endoscopy reduces the rebleeding rate and the need for surgical haemostasis	**Evidence Ia**
Following successful endoscopic therapy, PPI treatment should be given as an intravenous bolus followed by continuous infusion, reducing rebleed-	**Evidence Ib**

ing rate and mortality	
PPI should not be used prior to endoscopy in patients presenting with upper gastrointestinal bleeding	**Evidence Ia**
Pause ASA, clopidogrel, anticoagulation (AC) therapy, NSAID and SSRI	**Evidence III**
In the case of Forrest I-IIb ulcers without rebleeding, low-dose ASA can be resumed after 24 hours, during simultaneous high-dose PPI infusion	**Evidence Ib**
Nutrition	
Patients with Forrest IIc-III ulcers are allowed a normal diet after endoscopy	**Evidence IV**
Patients who have been treated endoscopically are allowed a liquid diet for the first 24 hours after the procedure and then an unrestricted diet	**Evidence IV**
Discharge	
Patients with Forrest IIc-III ulcers and no haemodynamic disturbance or serious comorbidity can often be discharged within a day of completing endoscopy	**Evidence Ib**
Patients with ulcers requiring endoscopic treatment are discharged on the basis of case-by-case judgement, but generally after 72 hours' PPI infusion at the earliest	**Evidence IV**
Aftercare	
All patients with peptic ulcer should be tested for Helicobacter pylori	**Evidence Ia**
If a satisfactory number of biopsies (5-7) has not been taken from patients with gastric ulcers or the experienced endoscopist is in doubt about possible malignancy, control gastroscopy must be carried out	**Evidence IV**
Patients in need of continued ASA or NSAID treatment should be put on prophylactic treatment with PPI at standard dosage	**Evidence Ib**
The combination of 75mg ASA and PPI should be preferred to monotherapy	**Evidence II**
with clopidogrel in patients needing anti-platelet therapy on the basis of indications other than coronary stents	

Quick guide

Admission and initial resuscitation

- Patients are assessed and managed in accordance with the ABCDE principles
- A minimum of two large peripheral IV lines are established
- In the event of shock, patients are treated with rapid infusion of 1,000-2,000 ml isotonic NaCl
- In the event of life-threatening bleeding, balanced blood component therapy in the proportions erythrocytes 3 : fresh frozen plasma 3 : platelets 1 is initiated as quickly as possible.
- In medical history, information about haematemesis, melaena, haematochezia, syncope, NSAID/ASA/vitamin K antagonists/SSRI intake, comorbidity or previous intervention on abdominal aorta should be obtained

Initial monitoring

- Heart rate, blood pressure, saturation, respiratory rate, diuresis and level of consciousness should be monitored every 15 min until the patient has stabilized and then once hourly
- Administration of fluids and blood should be documented on a dedicated chart
- Patients should be assessed and managed in a dedicated unit with specially trained staff

Timing of endoscopy

- Should generally be undertaken within 24 hours
- If severe bleeding is suspected, endoscopy within 12 hours is recommended
- If the patient's circulation cannot be stabilized, urgent endoscopy is performed on vital indication

Endoscopic treatment

- Forrest type I-IIb ulcers should be treated endoscopically.
- In most situations injection of 10-25 ml adrenaline-saline is recommended as the first modality in order to facilitate inspection of the bleeding site
- Endoscopic injection of adrenaline-saline should always be supplemented with a secondary therapeutic modality, usually in the form of a contact thermal probe or hemoclip

Invasive procedures

- If primary haemostasis cannot be achieved endoscopically, immediate transcatheter arterial embolization (TAE) is recommended

- If TAE is unavailable, immediate laparotomy, transfixion and ligation of the bleeding vessel is performed

Rebleeding

- Rebleeding should initially be treated by repeat endoscopy, if technically possible.
- In the event of further rebleeding, TAE, surgery or repeated endoscopic treatment is considered.

Initial pharmacological treatment

- Pause any ASA, NSAID, clopidogrel, vitamin K antagonist and SSRI treatment
- Low-risk ulcers (Forrest IIc-III) are treated with oral standard-dosage PPI. Ulcers requiring endoscopic treatment are treated with high-dose PPI given intravenously as bolus followed by continuous infusion for 72 hours
- Helicobacter pylori positive patients are given eradication therapy
- Patients who have had surgical haemostasis performed must be treated with low-molecular heparin and compression stockings postoperatively

References

1. Det nationale indikatorprojekt. Blødende gastroduodenalt ulcus – Tværfaglig national klinisk retningslinje for diagnostik, behandling og pleje [Danish National Indicator Project: Bleeding gastroduodenal ulcer – Interdisciplinary national clinical guideline for diagnosis, treatment and care]. http://www.nip.dk
2. Thim T, Krarup NH, Grove EL et al. ABCDE - systematisk tilgang til patienter med kritisk sygdom [ABCDE - systematic access to patients with critical illness]. Ugeskr Læger 2010;172:3264-3266.
3. ERC. Advanced Life Support. 5th ed., 2006.
4. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2007:CD000567.
5. National Board of Health, Denmark. Vejledning om blodtransfusion [Blood Transfusion Guideline]. http://www.sst.dk. 2007.
6. Sanders DS, Perry MJ, Jones SG et al. Effectiveness of an upper-gastrointestinal haemorrhage unit: a prospective analysis of 900 consecutive cases using the Rockall score as a method of risk standardisation. Eur J Gastroenterol Hepatol 2004;16:487-494.
7. Danish National Indicator Project, http://www.nip.dk
8. Laursen SB, Schaffalitzky de Muckadell OB. Det optimale tidspunkt for gastroskopi ved svær ulcusblødning er ikke fastlagt. Ugeskr Laeger 2011;173:1130-4.
9. Lin HJ, Wang K, Perng CL et al. Early or delayed endoscopy for patients with peptic ulcer bleeding: a prospective randomized study. J Clin Gastroenterol 1996;22:267-71.
10. Cook DJ, Guyatt GH, Salena BJ et al. Endoscopic therapy for acute nonvariceal upper gastrointestinal haemorrhage: a meta-analysis. Gastroenterology 1992;102:139-48.
11. Barkun AN, Bardou M, Kuipers EJ et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern with 2010;152:101-113.
12. Kahl CJ, Jensen DM, Sung JJY et al. Endoscopic Therapy Versus Medical Therapy for Bleeding Peptic Ulcer with Adherent Clot: A Meta-analysis. Gastroenterology 2005;129:855–862.
13. Choudari CP, Palmer KR. Endoscopic injection therapy for bleeding peptic ulcer; a comparison of adrenaline alone with adrenaline plus ethanolamine oleate. Gut 1994;35:608-610.
14. Chung SC, Leong HT, Chan AC et al. Epinephrine or epinephrine plus alcohol for injection of bleeding ulcers: a prospective randomized trial. Gastrointest Endosc 1996;43:591-595.
15. Llach J, Bordas JM, Salmeron JM et al. A prospective randomized trial of heater probe thermocoagulation versus injection therapy in peptic ulcer haemorrhage. Gastrointest Endosc 1996;43:117-120.
16. Rollhauser C, Fleischer DE. Current status of endoscopic therapy for ulcer bleeding. Baillieres Best Pract Res Clin Gastroenterol 2000;14:391-410.
17. Lin HJ, Hsieh YH, Tseng GY et al. A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. Gastrointest Endosc 2002;55:615-619.
18. Liou TC, Lin SC, Wang HY et al. Optimal injection volume of epinephrine for endoscopic treatment of peptic ulcer bleeding. World J Gastroenterol 2006;12:3108-3113.
19. Park CH, Lee SJ, Park JH et al.Optimal injection volume of epinephrine for endoscopic prevention of recurrent peptic ulcer bleeding. Gastrointest Endosc 2004;60:875-80.
20. Matthewson K, Swain CP, Bland M et al. Randomized comparison of Nd YAG laser, heater probe, and no endoscopic therapy for bleeding peptic ulcers. Gastroenterology 1990; 98:1239-44.
21. Hui WM, Ng MM, Lok AS et al. A randomized comparative study of laser photocoagulation, heater probe, and bipolar electrocoagulation in the treatment of actively bleeding ulcers. Gastrointest Endosc 1991;37:299-304.

22. Laine L. Multipolar electrocoagulation in the treatment of active upper gastrointestinal tract haemorrhage. A prospective controlled trial. N Engl J Med 1987;316:1613-7.
23. Cipolletta L, Bianco MA, Marmo R et al. Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: a prospective and randomized trial. Gastrointest Endosc 2001;53:147-51.
24. Lin HJ, Hsieh YH, Tseng GY et al. A prospective, randomized trial of endoscopic Hemoclip versus heater probe thermocoagulation for peptic ulcer bleeding. Am J Gastroenterol 2002;97:2250-4.
25. Lin HJ, Perng CL, Sun IC et al. Endoscopic Hemoclip versus heater probe thermocoagulation plus hypertonic saline-epinephrine injection for peptic ulcer bleeding. Dig Liver Dis 2003;35:898-902.
26. Yuan Y, Wang C, Hunt RH. Endoscopic clipping for acute nonvariceal upper-GI bleeding: a meta-analysis and critical appraisal of randomized controlled trials. Gastrointest Endosc 2008;68:339-51.
27. Levy J, Khakoo S et al. Fatal injection sclerotherapy of a bleeding peptic ulcer (letter). Lancet 1991; 337:504.
28. Loperfido S, Patelli G et al. Extensive necrosis of gastric mucosa following injeciont therapy of bleeding peptic ulcer (letter). Endoscopy 1990; 22:285-286.
29. Chau CH, Siu WT, Law BK et al. Randomized controlled trial comparing epinephrine injection plus heat probe coagulation versus epinephrine injection plus argon plasma coagulation for bleeding peptic ulcers. Gastrointest Endosc 2003;57:455-461.
30. Cipolletta L, Bianco MA, Rotondano G, Piscopo R, Prisco A, Garofano ML. Prospective comparison of argon plasma coagulator and heater probe in the endoscopic treatment of major peptic ulcer bleeding. Gastrointest Endosc 1998;48:191-195.
31. Taghavi SA, Soleimani SM, Hosseini-Asl SM et al. Adrenaline injection plus argon plasma coagulation versus adrenaline injection plus Hemoclips for treating high-risk bleeding peptic ulcers: a prospective, randomized trial. Can J Gastroenterol 2009;23:699-704.
32. Vergara M, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. Cochrane Database Syst Rev 2007;CD005584.
33. Marmo R, Rotondano G, Piscopo R et al. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. Am J Gastroenterol 2007;102:279-289.
34. Calvet X, Vergara M, Gisbert JP et al. Dual versus endoscopic monotherapy in bleeding peptic ulcers. Am J Gastroenterol. 2007;102:1826-7; author reply 1827-8.
35. Bai Y, Zhaoshen L. Results of meta-analysis should be interpreted with much caution. Am J Gastroenterol 2007;102:1826; author reply 1827-8.
36. Adler DG. Is dual therapy superior to monotherapy for the endoscopic treatment of patients with high-risk peptic ulcer bleeding Nat Clin Pract Gastroenterol Hepatol 2007;4:480-1.
37. Barkun AN, Martel M, Toubouti Y et al. Endoscopic haemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses. Gastrointest Endosc 2009;69:786-99.
38. Ripoll C, Banares R, Beceiro I et al. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. J Vasc Interv Radiol 2004;15:447-450.
39. Wong TC, Wong KT, Chiu PW et al. A comparison of angiographic embolization with surgery after failed endoscopic haemostasis to bleeding peptic ulcers. Gastrointest Endosc 2011;73:900-8.
40. Loffroy R, Rao P, Ota S et al. Embolization of acute nonvariceal upper gastrointestinal haemorrhage resistant to endoscopic treatment: results and predictors of recurrent bleeding. Cardiovasc Intervent Radiol 2010;33:1088-100.
41. Millat B, Hay JM, Valleur P et al. Emergency surgical treatment for bleeding duodenal ulcer: oversewing plus vagotomy versus gastric resection, a controlled randomized trial. French Associations for Surgical Research. World J Surg 1993;17:568-573.
42. Poxon VA, Keighley MR, Dykes PW et al. Comparison of minimal and conventional surgery in patients with bleeding peptic ulcer: a multicentre trial. Br J Surg 1991;78:1344-1345.
43. Saunders WB. Core Topics in general and emergency surgery. 2 ed2001.
44. Lau JY, Sung JJ, Lam YH et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999;340:751-756.
45. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2006:CD002094.
46. Focareta R, Ciarleglio A, Piai G et al. Proton-pump inhibitor and acute peptic ulcer bleeding: effectiveness of oral esomeprazole vs. intravenous omeprazole in reducing the risk of recurrent bleeding [Abstract]. Dig Liver Dis 2004;36:S250.
47. Jang J, Dong S, Jung J et al. High-dose oral proton pump inhibitor is as effective as intravenous administration in the aspect of increasing pH and reducing rebleeding after endoscopic treatment of

bleeding peptic ulcers [Abstract]. Gastroenterology 2006;103:A467.
48. Bajaj JS, Dua KS, Hanson K et al. Prospective, randomized trial comparing effect of oral versus intravenous pantoprazole on rebleeding after nonvariceal upper gastrointestinal bleeding: a pilot study. Dig Dis Sci 2007;52:2190-4.
49. Dorward S, Sreedharan A, Leontiadis GI et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev 2006: CD005415.
50. Biondi-Zoccai GG, Lotrionte M, Agostoni P et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667-2674.
51. Sung JJ, Lau JY, Ching JY et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern with 2010;152:1-9.
52. Gluud LL, Klingenberg SL, Langholz SE. Systematic review: tranexamic acid for upper gastrointestinal bleeding. Aliment Pharmacol Ther 2008;27:752-758.
53. Oates-Whitehead RM, D'Angelo A, Mol B. Anticoagulant and aspirin prophylaxis for preventing thromboembolism after major gynaecological surgery. Cochrane Database Syst Rev 2003:CD003679.
54. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2009:CD004318.
55. Wille-Jorgensen P, Rasmussen MS, Andersen BR et al. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. Cochrane Database Syst Rev 2003:CD001217.
56. De Lédinghen V, Beau P, Mannant PR et al. When should patients with bleeding peptic ulcer resume oral intake? A randomized controlled study. Gastroenterol Clin Biol 1998;22:282-5.
57. Cipolletta L, Bianco MA, Rotondano G et al. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. Gastrointest Endosc 2002;55:1-5.
58. Hsu PI, Lai KH, Lin XZ et al. When to discharge patients with bleeding peptic ulcers: a prospective study of residual risk of rebleeding. Gastrointest Endosc 1996;44:382-7.
59. Longstreth GF, Feitelberg SP. Successful outpatient management of acute upper gastrointestinal haemorrhage: use of practice guidelines in a large patient series. Gastrointest Endosc 1998;47:219-22.
60. Sung JJ, Barkun A, Kuipers EJ et al. Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. Ann Intern with 2009;150: 455-64.
61. Lau JY, Sung JJ, Lee KK et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343:310-6.
62. Jensen DM, Pace SC, Soffer E et al. Continuous infusion of pantoprazole versus ranitidine for prevention of ulcer rebleeding: a U.S. multicenter randomized, dual-blind study. Am J Gastroenterol 2006; 101:1991-9.
63. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database Syst Rev 2006:CD003840.
64. Bytzer P. Endoscopic follow-up study of gastric ulcer to detect malignancy: is it worthwhile? Scand J Gastroenterol 1991;26:1193-9.
65. Lanas A, Garcia-Rodriguez LA, Arroyo MT et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006;55:1731-1738.
66. Chan FK, Chung SC, Suen BY et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001;344:967-973.
67. Chan FK, Ching JY, Hung LC et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352:238-244.
68. Lai KC, Chu KM, Hui WM et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006;4:860-865.
69. Hsiao FY, Tsai YW, Huang WF et al. A comparison of aspirin and clopidogrel with or without proton pump inhibitors for the secondary prevention of cardiovascular events in patients at high risk for gastrointestinal bleeding. Clin Ther 2009;31:2038-2047.
70. Juurlink DN, Gomes T, Ko DT et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-718.

Appendix

Members of the working group of the Danish National Indicator Project for acute gastrointestinal surgery:

Jørgen Bendix
Daniel Buck
Ellen-Margrethe Jacobsen
Anders Gadegaard Jensen

Henrik Stig Jørgensen
Finn Kallehave
Birgitte Randrup Krog
Morten Hylander Møller
Ann-Sophie Nielsen
Dorthe Oxholm
Steffen Rosenstock
Ove B. Schaffalitzky de Muckadell
Mona Skarbye
Susanne Stenkær
Reimar W. Thomsen