BLEEDING OF VARIABLE SEVERITY CAN OCCUR ANYWHERE IN THE GASTROINTESTINAL TRACT. UPPER GASTROINTESTINAL (GI) BLEEDING IS DEFINED AS BLEEDING PROXIMAL TO THE LIGAMENT OF TREITZ.

GENERAL OBSERVATIONS

The incidence of upper gastrointestinal bleeding is approximately 50 per 100,000 persons per year (1). The mortality of this condition is between 5% and 11% (2). The main sources of bleeding are peptic ulcers, esophagitis, drug-induced mucosal damage, sequelae of portal hypertension (esophageal varices, varices of the gastric fundus, portal hypertensive gastropathy), vascular anomalies, traumatic and postoperative lesions, and tumors (see box 1). The classic clinical signs are the regurgitation or vomiting of blood (hematemesis) and black, tarry stool (melena). Severe, brisk bleeding can also present with the passage of bright red blood per rectum (hematochezia). Insidious upper gastrointestinal bleeding can present with non-specific signs such as fatigue, prostration, shortness of breath, or angina pectoris.

Occasionally, the only finding pointing to a gastrointestinal hemorrhage is a laboratory result, such as iron-deficiency anemia or a positive test for occult blood in the stool. The stool can be tarry if 50 to 100 mL of blood are lost per day. Hemodynamically relevant manifestations, e.g., hypotension in a supine patient, arise after loss of 20% to 25% of the total intravascular blood volume and indicate the presence of massive hemorrhage. Patients with orthostatic tachycardia and hypotension have lost at least 10% to 20% of their intravascular blood volume. Alongside these hemodynamic parameters indicating the severity of the hemorrhage, a number of clinical signs provide clues to its localization as well as to possible accompanying illnesses:

- Tarry stool and hematemesis indicate upper gastrointestinal bleeding.

THE CLASSIC SIGNS OF GASTROINTESTINAL BLEEDING ARE

- Regurgitation or vomiting of blood (hematemesis)
- Tarry stool

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KEY WORDS: GASTROINTESTINAL BLEEDING, MELENA STOOL, HEMATEMESIS, GASTROESOPHAGEAL VARICES, BANDING, ENDOSCOPY
Hematochezia indicates lower gastrointestinal bleeding or massive bleeding distal to the pylorus of the stomach.

Ascites and jaundice indicate hepatic failure and imply that the source of bleeding may be dilated venous collaterals in a patient with hepatic cirrhosis.

The following points in the history require attention:

- Has the patient regularly been taking any medications that can provoke hemorrhage, such as non-steroidal anti-inflammatory drugs (NSAID), anticoagulants, or platelet aggregation inhibitors?
- Has the patient ever had a similar episode before (variceal hemorrhage, diverticular hemorrhage)?
- Have any prostheses been inserted that might bear a causal relationship to the hemorrhage (coronary stents and platelet aggregation inhibitors, cardiac valvular prostheses and anticoagulants, aortic prostheses with the risk of an aorto-intestinal fistula)?

If endoscopy cannot be performed immediately, two bedside tests may be useful, both of which are relatively specific for upper intestinal bleeding, though not very sensitive:

1. rectal examination with examination of the stool for its color and consistency (melena);
2. the insertion of a nasogastric tube to diagnose or exclude severe upper gastrointestinal hemorrhage.

The initial laboratory tests include a blood count, INR, PTT, electrolytes, creatinine, and blood typing and cross-matching in case transfusion should be necessary. Every patient with a severe intestinal hemorrhage, particularly if esophageal varices are suspected or the hemorrhage is already hemodynamically significant, should first be hemodynamically stabilized in an intensive care or step-down unit. Further diagnostic measures should be undertaken once the patient is hemodynamically stable.

**Clinical assessment and risk estimation**

The most important initial assessment is the measurement of the patient’s pulse and blood pressure. The physical examination can also provide clues to the source of the hemorrhage. The main risk factors that are evident on clinical examination are hemodynamic instability, a drop of the hematocrit by more than 6%, and any evidence of active bleeding (hematemesis, hematochezia).

**Important points in the history**

- Medications that promote bleeding?
- Any earlier episodes of hemorrhage?
- Are there any implanted prostheses that might be causally related to the hemorrhage?

**Initial treatment**

Every patient with a severe gastrointestinal hemorrhage must first be hemodynamically stabilized.
A number of classification systems have been proposed for assessing the patient's prognosis. Unfavorable prognostic factors include the following:

- Age over 65 years
- More than two concomitant illnesses
- An unfavorable site of bleeding (posterior wall of the duodenal bulb)
- Clinical signs of severe bleeding (hematemesis, hematochezia)
- Hemodynamic instability
- Active bleeding during endoscopy

A number of scoring systems have been developed to assess the prognosis after bleeding from peptic ulcer disease (Baylor Score, Rockall Score, Cedars-Sinai Index). It has not yet been conclusively determined which of these scoring systems is best in clinical practice (3).

**Diagnostic assessment and the causes of hemorrhage**

The most important diagnostic step is upper gastrointestinal endoscopy. In cases of hemodynamically relevant hemorrhage, endoscopy should be performed as soon as the patient has been clinically stabilized (although no controlled studies on the ideal timing of endoscopy are yet available). A standard endoscope is used, or, if the hemorrhage is massive, an endoscope with a wide working tube. If a rare source of hemorrhage is suspected, such as bleeding from the papilla, the device can be switched to one with side-view optics. The source of bleeding can be localized by endoscopy in about 90% of patients with upper gastrointestinal hemorrhage (2).

**Sources of bleeding and treatment**

**Bleeding ulcers**

Bleeding from ulcers is the most common type of upper GI bleeding (30% to 40%, though the percentage estimates vary widely). About 60% of bleeding ulcers are located in the duodenum (figure 1), while 40% are in the stomach. Bleeding ulcers are classified by the Forrest criteria (4) (box 3); this classification provides a means of estimating the risk of continued or recurrent bleeding if purely supportive treatment is provided, without local hemostasis (table). All patients with active bleeding or with endoscopic signs of bleeding, such as a vascular stump or an adherent blood clot, should be treated endoscopically, e.g., by the injection of suprarenin solution (1:10 000), local argon plasma coagulation (APC), or clipping of the bleeding vessel with one or more endoclips. Adherent clots should be irrigated away; if a clot cannot be removed by irrigation, one can first inject suprarenin into the underlying vessel (to prevent hemorrhage), then remove the clot with a polypectomy loop and, finally, treat the lesion beneath the clot endoscopically (5). Initial hemostasis is successful in 70% of patients, including high-risk patients (Forrest Ia hemorrhage from an ulcer on the posterior duodenal wall).

Multiple meta-analyses of clinical trials have confirmed that endoscopic treatment significantly improves patients' prognosis with respect to recurrent hemorrhage and the need for transfusions and surgery (level 1a evidence, grade A recommendation). An older meta-analysis (6) already showed that local endoscopic therapy raises the probability of not sustaining a recurrent hemorrhage, or of not requiring surgery, by 60%.

It is still unclear what the best form of local treatment is among the various ones that are currently available. Combination therapy is probably the most effective approach, e.g., suprarenin injection followed by clipping (7; level 1b evidence, grade A recommendation [see also box 2]).

Controlled studies have shown that the administration of proton pump inhibitors for 72 hours right after endoscopic intervention significantly lowers the risk of recurrent hemorrhage (8). Omeprazole is the best-studied proton pump inhibitor; 80 mg are given initially, followed by a continuous infusion of 8 mg/hour. The

**Poor prognostic signs**

- Age > 65 years
- More than two types of concomitant illness
- Hemodynamic instability
- Brisk, active bleeding during endoscopy

**Diagnostic assessment**

The most important method is endoscopy of the upper gastrointestinal tract with a standard endoscope, or, in the case of active bleeding, an endoscope with a wide working tube.
rate of recurrent hemorrhage was 6.7% in the PPI group, versus 22.5% in the placebo group. It is unclear, however, whether PPI infusion also lowers mortality (level 1b evidence, grade A recommendation). Another study has shown that a single daily dose of 20 mg of omeprazole works just as well as the regime described above (level 1b evidence, grade A recommendation) (9). Oral administration may even suffice (level 1b evidence, grade A recommendation) (10). In a very recent study, Lau et al. found that a high dose of omeprazole given before endoscopy raises the likelihood of success of endoscopic therapy (level 1b evidence, grade A recommendation) (11). As for proton pump inhibition therapy for bleeding ulcers, two current Cochrane analyses on the subject were published in 2006 (12, 13). In the analysis by Leontiadis et al., only high-dose PPI administration was found to lower the rate of surgical intervention significantly. High-dose therapy was defined, in this context, as the administration of more than 120 mg over 24 hours, e.g., as an 80 mg bolus followed by a continuous infusion of 8 mg per hour (level 1a evidence, grade A recommendation) (13). Neither of these two meta-analyses showed a reduction in mortality (12, 13). It must be pointed out, however, that some of the studies included in these analyses were performed in Asian countries. It is known that persons of Asian ethnic origin metabolize PPI in a different way than persons of European origin; thus, the study results are not necessarily generalizable to patients in Europe.

Though these data are encouraging, there remains controversy as to whether proton pump inhibitors ought to be given intravenously after successful hemostasis by endoscopic therapy. A prospective international study is currently being performed to answer this question; its results have not yet been announced.

In the authors’ institution, patients with bleeding ulcers are initially given 40 mg of omeprazole twice daily, or an equivalent amount of another proton pump inhibitor, intravenously for at least three days. The dose is adjusted thereafter depending on the size of the ulcer and the further course of healing, until the route of administration is finally switched from intravenous to oral.

After initially successful treatment, it is important to lower the risk of recurrent hemorrhage permanently. The successful eradication of an associated Helicobacter pylori infection lowers the risk of reappearance of an ulcer in the first year after hemorrhage to less than 5% (14) (level 1b evidence, grade A recommendation).

Sources of hemorrhage
Ulcers are the most common source of upper gastrointestinal hemorrhage (35%).

Treatment
Local endoscopic therapy raises the probability of not suffering any further hemorrhages, and of not needing surgery, by 60%.
Therefore, every patient should already be tested for Helicobacter pylori at the initial endoscopy. The sensitivity of the rapid Helicobacter pylori test has not yet been affected when the initial endoscopy is performed, but then drops considerably once PPI treatment is begun. At the same time, the possibility of a drug-induced ulcer must be definitively confirmed or ruled out. If non-steroidal anti-inflammatory drugs (NSAID) have played a contributory role in the hemorrhage, they should either be discontinued or – if they are absolutely necessary – continued in combination with a PPI. It is not yet known for certain whether it is better to give a COX-2-selective NSAID together with a PPI than to give a non-selective COX inhibitor together with a PPI. In any case, this combination was used successfully in high-risk patients in a recent study (15) with a median follow-up interval of 13 months. It is important to point out that this study was performed in Hong Kong, and its results are not necessarily generalizable to Germany. The patients in the study population were of Asian descent and therefore metabolized medications differently from European patients; thus, the same study, if performed in Europe, might have had a different result. Other pharmacological therapies aimed at stopping hemorrhage, e.g., the administration of tranexamic acid, somatostatin, and analogues of these substances, have been found to have only a small effect, if any, and are not currently a part of standard care.

In a few studies, the use of a motilin agonist (erythromycin 250 mg IV) before endoscopy has been found to improve the conditions for emergency endoscopy to a significant degree, because it speeds the passage of blood and clot through the stomach (16) (level 2b evidence, grade B recommendation).

It is difficult to say under what circumstances surgery is indicated, because there are no prospective, controlled studies to provide a reliable answer to this question (17). Surgery is certainly indicated, however, when any of the following is the case:
- when the patient cannot be hemodynamically stabilized despite adequate volume replacement and medical therapy,
- when recurrent hemorrhage occurs despite initial stabilization by endoscopic treatment and re-endoscopy, or
- when there is persistent hemorrhage requiring the transfusion of more than three units of erythrocyte concentrate per day.

Surgical consultation should always be obtained for patients with severe, active hemorrhage.

Interventional radiological techniques can be an alternative to surgery when the necessary apparatus and trained personnel are at hand. Selective catheterization and angiography can be used to localize the bleeding vessel, which can then be embolized, e.g., with metallic coils (18). However, 10% to 20% of patients treated in this way will have a recurrent hemorrhage within 72 hours.

**Risk reduction**
High-dose PPI therapy significantly lowers the rate of surgical intervention.

**The risk of recurrence**
The successful eradication of an associated Helicobacter pylori infection reduces the risk of appearance of a new ulcer in the first year after an ulcer-related hemorrhage to less than 5%.
**Hemorrhage from collateral vessels in portal hypertension**

Hemorrhage from collateral vessels, usually esophageal varices, in the setting of portal hypertension is one of the more common causes of upper gastrointestinal hemorrhage (figure 2) (19). The prognosis is poor. Up to 30% of these patients, most of whom have hepatic cirrhosis, die as a result of the initial bleed (20). As soon as the clinical suspicion of a variceal hemorrhage arises, vasoactive treatment should be initiated, e.g., with 1.5 mg of terlipressin IV every 4 to 6 hours in a 70-kg patient (level 1a evidence, grade A recommendation), unless contraindicated by severe coronary heart disease or other comorbidities. This treatment is continued for 2 to 5 days (21). The same holds for antibiotic prophylaxis, e.g., with ciprofloxacin 500 mg po bid (22). The administration of antibiotics lowers the recurrence rate (23) (level 1b evidence, grade A recommendation). In one study, only 4 of 59 patients treated with antibiotics had a recurrent hemorrhage within 7 days of the initial bleed, as compared with 21 of 61 patients not treated with antibiotics (23).

Endoscopy should be performed as rapidly as possible in all patients in whom variceal bleeding is suspected. If active variceal bleeding is found, or if endoscopy reveals varices and blood in the stomach without any other evident source of hemorrhage, then endoscopic therapy should be provided immediately. This usually involves ligation of the varices.

Because varices of the gastric fundus cannot be treated safely by ligation, Histoacryl (n-butyl-2-cyanoacrylate) is injected into them instead (level 1b evidence, grade A recommendation).

If active variceal bleeding cannot be stopped endoscopically, local balloon tamponade must be performed as a temporizing measure, for no longer than 24 hours (level 4 evidence, grade C recommendation). Very recently, soft endoluminal stents have also been used to compress varices (figure 3). Only limited experience has been obtained with this technique to date.

Patients whose acute variceal bleeding persists despite endoscopic therapy can be treated by the insertion of a transjugular intrahepatic porto-systemic stent shunt (TIPS) (level 2b evidence, grade B recommendation). In the authors’ institution, the placement of an “emergency TIPS” has obviated the need for “emergency shunt surgery” in most patients. Nonetheless, this procedure does not reduce mortality to any significant degree for patients with severely decompensated hepatic cirrhosis, even if the bleeding can be successfully stopped.

**Mallory-Weiss tears**

Deep, bleeding tears of the mucosa at the gastro-esophageal junction are found in 5% to 10% of all patients.

**Indications for surgery**

- Hemodynamic instability despite adequate volume resuscitation
- Recurrent hemorrhage after two endoscopic hemostatic procedures
- Persistent bleeding requiring the transfusion of more than three units of red cells per day

**Bleeding from esophageal varices**

Up to 30% of patients die from their initial hemorrhage.
with upper gastrointestinal bleeding. Usually, tearing of this type is precipitated by vomiting or coughing fits. Alcoholic persons are predisposed to Mallory-Weiss tears. Often, the bleeding stops spontaneously. If the lesion is actively bleeding, hemostasis should be obtained via endoscopy, either with the application of clips or with rubber-band ligation (24) (level 2b evidence, grade B recommendation).

**Hemorrhagic-erosive changes**

Hemorrhagic-erosive changes can occur in the esophagus and in the stomach. Such changes in the esophagus are often due to reflux esophagitis or to medications; in the stomach, they are often associated with non-steroidal anti-inflammatory drugs (NSAID), alcoholism, or stress lesions in patients receiving intensive care. Stress-induced gastric lesions most

**Varices of the gastric fundus**

Varices of the gastric fundus cannot be safely treated with ligation and are, therefore, treated by the injection of tissue sealants.

**TIPS**

The insertion of a transjugular intrahepatic portal-systemic stent shunt (TIPS) is a therapeutic option when the endoscopic treatment of an acute variceal hemorrhage is unsuccessful.
commonly occur in patients with burns or neurological illnesses. Local hemostasis is only rarely needed in such cases. The most important form of treatment here consists of recurrence prophylaxis with proton pump inhibitors.

**Rarer causes of upper gastrointestinal hemorrhage**

If endoscopy initially fails to reveal any source of hemorrhage even though an upper gastrointestinal bleed has unquestionably occurred, as manifested by the finding of blood or blood clots in the lumen of the gastrointestinal tract, then rarer causes of hemorrhage should be considered in the differential diagnosis (*box 1*). Hemorrhages from large, aberrant vascular ectasias with small overlying mucosal defects, usually in the gastric fundus (Dieulafoy lesion, illustrated in *figure 4*) are particularly dangerous. These have been treated successfully with injection therapy and endoclips ap- plication as well as with rubber-band ligation (level 3b evidence, grade C recommendation).

Rarer, gastric antral vascular ectasia (the GAVE syndrome, also called “watermelon stomach”) can be the cause of a gastrointestinal bleed (*figure 5*). GAVE syndrome often arises in connection with portal hypertension. Repeated argon gas plasma coagulation is a treatment option with a good chance of success (level 4 evidence, grade C recommendation).

Another rare cause of upper gastrointestinal hemorrhage is bleeding from the hepato-bilio-pancreatic system (at endoscopy, blood is seen to be coming out of the papilla). Duodenal diverticula, if present, can also be a site of hemorrhage. Like colonic diverticula, these are treated with injection therapy and/or endoclips.

Vasculitis should be considered in the differential diagnosis if the patient has cutaneous changes and the autoantibodies that are typical of this entity. Vasculitis of the intermediate-sized and small vessels, as is seen in Churg-Strauss syndrome or polyarteritis nodosa, can cause ischemic ulceration and, therefore, hemorrhage. The treatment is directed at the underlying illness; endoscopic intervention is rarely needed to control the bleeding.

Aorto-enteric fistulae usually arise after surgery for an aortic aneurysm and are a source of special danger. This possibility is usually suggested by the patient’s history or by the findings of computed tomography. There is usually no way to treat a bleeding aorto-enteric fistula endoscopically and the patient must therefore be taken to surgery immediately.

The authors have developed a diagnostic and therapeutic algorithm for upper GI bleeding that is currently in use in their institution (*figure 6*).

**Conclusion**

Gastrointestinal bleeding is frequently encountered in clinical practice and becomes more common with advancing age. It is vitally important to recognize the patients that are in acute danger from hemorrhage as soon as they present to medical attention. These patients should be hemodynamically stabilized and should then undergo endoscopy as soon as possible thereafter. If the source of the bleeding is found, it can usually be directly treated with endoscopic therapy.

**Conflict of interest statement**

Dr. Heller has received lecture honoraria from Meduna Arzneimittel GmbH. Dr. Lammert has received lecture honoraria from the Falk Foundation. Prof. Sauerbruch has received lecture honoraria from the Falk Foundation and third-party funds from various companies for continuing medical education events at the University of Bonn Medical Department. Dr. Biecker and Dr. Schmitz state that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

**REFERENCES**


Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
Which of the following simple diagnostic measures may yield clues to the source of a gastrointestinal hemorrhage?

- a) Examination of the pupils and carbon-14 breathing test
- b) Esophageal manometry and test for occult blood in the stool
- c) Insertion of a nasogastric tube and rectal stool examination
- d) Venous and arterial blood gas analysis
- e) Blood count and ECG

**Question 2**
What is the most common cause of upper gastrointestinal bleeding?

- a) Duodenal ulcer
- b) Gastric ulcer
- c) Esophageal ulcer
- d) Reflux esophagitis
- e) Esophageal varices

**Question 3**
Which of the following clinical signs is seen in upper gastrointestinal bleeding?

- a) Hematemesis
- b) Fall of body temperature
- c) Hemosiderosis
- d) Bradycardia
- e) Rise in blood pressure

**Question 4**
What is the percentage risk of recurrent hemorrhage after a Forrest IIb bleed without local endoscopic treatment?

- a) 5% to 10%
- b) 15% to 20%
- c) 25% to 30%
- d) 35% to 40%
- e) 45% to 50%

**Question 5**
Which of the following statements about local endoscopic therapy for gastrointestinal bleeding is correct?

- a) Local endoscopic therapy reduces the need for surgery.
- b) Local endoscopic therapy is of lesser importance than surgical treatment.
- c) Local endoscopic therapy is limited to the application of one particular method.
- d) Local endoscopic therapy can only be performed in the esophagus.
- e) Local endoscopic therapy is performed through a rigid endoscope.

**Question 6**
Which of the following statements about medical therapy for gastrointestinal bleeding is correct?

- a) Antibiotic prophylaxis after esophageal variceal bleeding improves survival.
- b) Antibiotic prophylaxis after gastric ulcer bleeding is indicated for patients over 80 years of age.
- c) Treatment with a proton pump inhibitor improves survival in patients with esophageal variceal bleeding.
- d) A Forrest IIa hemorrhage is treated with intravenous antibiotics.
- e) The administration of terlipressin causes arterial vasodilation in patients with gastrointestinal hemorrhage.

**Question 7**
Which of the following techniques is used during endoscopic hemostasis?

- a) The injection of hyaluronic acid
- b) The application of endoclips
- c) The application of tamponades
- d) The injection of botulinum toxin solution
- e) Embolization with starch spheres

**Question 8**
Which of the following parameters indicates a poor prognosis?

- a) Advanced age of the patient
- b) Uncomplicated ventricular ulcer
- c) Helicobacter pylori colonization
- d) Stable blood pressure
- e) No active bleeding seen at endoscopy

**Question 9**
Which of the following statements about varices is correct?

- a) Varices of the gastric fundus are surgically removed in a very invasive operation on the stomach.
- b) The placement of a balloon catheter is the treatment of choice for variceal hemorrhage.
- c) A Mallory-Weiss lesion is a varix of the duodenum.
- d) Esophageal varices are often the cause of upper gastrointestinal hemorrhage.
- e) For a patient with variceal bleeding, endoscopy should be deferred until the bleeding stops.

**Question 10**
Which of the following statements about the eradication of an associated Helicobacter pylori infection in a patient with a gastrointestinal hemorrhage is correct?

- a) The eradication of an associated Helicobacter pylori infection is the treatment of choice for esophageal varices if no other source of hemorrhage is found.
- b) The successful eradication of an associated Helicobacter pylori infection reduces the risk of recurrent hemorrhage in the first year after the initial bleed to less than 5%.
- c) Helicobacter pylori eradication after a Mallory-Weiss tear raises the probability of having no further hemorrhages by 60%.
- d) Randomized studies have refuted the hypothesis that successful Helicobacter pylori eradication after bleeding from ulcers is an effective treatment for this disease.
- e) The eradication of an associated Helicobacter pylori infection is not indicated in patients who are taking non-steroidal anti-inflammatory drugs.