Bleeding Duodenal Ulcer: Strategies in High-Risk Ulcers

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Keywords

Duodenal ulcer · Bleeding · Embolization · Surgery · Endoscopy

Abstract

Background: Acute peptic ulcer bleeding is still a major reason for hospital admission. Especially the management of bleeding duodenal ulcers needs a structured therapeutic approach due to the higher morbidity and mortality compared to gastric ulcers. Patient with these bleeding ulcers are often in a high-risk situation, which requires multidisciplinary treatment. **Summary:** This review provides a structured approach to modern management of bleeding duodenal ulcers and elucidates therapeutic practice in high-risk situations. Initial management including pharmacologic therapy, risk stratification, endoscopy, surgery, and transcatheter arterial embolization are reviewed and their role in the management of bleeding duodenal ulcers is critically discussed. Additionally, a future perspective regarding prophylactic therapeutic approaches is outlined. **Key Messages:** Beside pharmacotherapeutic and endoscopic advances, bleeding management of high-risk duodenal ulcers is still a challenge. When bleeding persists or rebleeding occurs and the gold standard endoscopy fails, surgical and radiological procedures are indicated to manage ulcer bleeding. Surgical procedures are performed to control hemorrhage, but they are still associated with a higher morbidity and a longer hospital stay. In the meantime, transcatheter arterial embolization is recommended as an alternative to surgery and more often replaces surgery in the management of failed endoscopic hemostasis. Future studies are needed to improve risk strat-

ification and therefore enable a better selection of high-risk ulcers and optimal treatment. Additionally, the promising approach of prophylactic embolization in high-risk duodenal ulcers has to be further investigated to reduce rebleeding and improve outcomes in these patients.

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Introduction

Gastrointestinal bleeding is still a common reason for hospital admission. While endoscopy is the therapeutic gold standard, especially in high-risk situations, a multidisciplinary approach is needed for the optimal treatment of patients. In 85% of the cases, the bleeding site is localized proximal to the ligament of Treitz and therefore classified as upper gastrointestinal bleeding (UGIB). Acute UGIB remains an important clinical problem, with incidence rates of 37–172 per 100,000 individuals [1–3]. Despite pharmacological and endoscopic advances, mortality remains high, i.e., up to 14% in recent decades; this might be the result of demographic changes, with older patients suffering from more comorbidities [2, 4]. Non-variceal bleeding is the most common cause of UGIB, whereas 31–67% of cases are caused by peptic ulcer disease (PUD) [2, 3, 5, 6]. PUD can be further divided into gastric ulcers and duodenal ulcers (DU), and DU bleed 1.3–2.3 times more frequently [1, 7–9]. Due to anatomical aspects, endoscopic therapy for bleeding DU can be very challenging, especially when the bleeding site is located on the posterior wall of the duodenal bulb. Additionally, the gastroduodenal artery (GDA) is located directly be-

hind the posterior duodenal wall, and erosion of this artery or its branches can result in massive bleeding and is associated with an increased risk of rebleeding [10]. So, it is not surprising that bleeding DU are associated with higher mortality, surgery, and readmission rates compared to gastric ulcers [11]. Therefore, it is especially crucial to know the current recommendations for UGIB management and recent studies in order to adhere to a systematic therapeutic approach. Additionally, it is essential in high-risk DU to manage bleeding when endoscopy fails and bleeding persists or recurs. It is the aim of this article to review the management of peptic ulcer bleeding with a focus on DU according to recent recommendations and studies. Additionally, extended treatment modalities in high-risk DU, which exhibit a particular multidisciplinary challenge, will be illustrated and discussed.

Management of Bleeding DU

Successful therapy for bleeding DU is characterized by an interdisciplinary approach, depending on the clinical appearance. DU therapy follows in its basic therapeutic procedures the management of bleeding peptic ulcers, which will be briefly summarized in this review. Figure 1 shows the basic workflow for ulcer management, which illustrates the involvement of an endoscopist, a surgeon, and an interventional radiologist at different stages of the therapeutic sequence.

Initial Management

Initial hemodynamic stabilization is the first step in the management of bleeding DU. Beside fluid substitution, transfusion of red blood cells should be considered to stabilize patients. Restrictive transfusion strategies have been implemented, but the timing and amount are still intensively discussed. Villanueva et al. [12] showed, in their RCT, that a restrictive hemoglobin threshold of 70 g/L was associated with significantly lower mortality and rebleeding rates compared to a liberal transfusion threshold of 90 g/L. A consecutive cluster randomized feasibility trial including 6 university hospitals also compared liberal (100 g/L) and restrictive transfusion thresholds (80 g/L). The authors did not find any differences in clinical outcomes, so a restrictive regime was not recommended [13]. Additionally, a meta-analysis of 5 RCT including 1,965 participants confirmed that restrictive transfusion is associated with a lower risk of all-cause mortality (RR = 0.65; 95% CI 0.44–0.97; $p = 0.03$) and rebleeding (RR = 0.58; 95% 0.40–0.84; $p = 0.004$) [14]. Of course, hemoglobin thresholds are of limited use in patients with massive ulcer bleeding, because hemodilution and a decrease in hemo-

Fig. 1. Schematic algorithm for the management of bleeding peptic ulcers.

globin levels exhibit a time shift regarding bleeding onset. For those reasons the management of patients with massive bleeding should adhere to local protocols.

Due to the increased use of antithrombotic medication in therapy for cardiovascular disease, an increasing number of patients with UGIB are now presenting with these drugs. A multicenter observational study showed that 44% of the patients were taking an antithrombotic drug, while 25% were taking even more than one [15]. Additionally, these drugs were also identified as a risk factor for developing UGIB [15, 16], but data on the optimal management of anticoagulation correction is sparse. For patients taking vitamin K antagonists, it was shown that endoscopic hemostasis can be also successfully achieved with an INR of 1.5–2.5 compared to patients without anticoagulation [17]. Therefore, current guidelines recommend correction of the INR to <2.5, provided that endoscopy is not delayed because of factor substitution [18, 19]. Additionally, an even higher number of patients takes direct oral anticoagulants (DOAC), which increase the risk of gastrointestinal bleeding [20]. Because of the fact that there are no clinical trials addressing DOAC management in patients with ulcer bleeding, current guidelines recommend temporarily pausing DOAC therapy.

Risk Stratification

Bleeding DU exhibit a wide variety of clinical manifestations from minor bleeding to hemorrhagic shock with a lethal end. Therefore, early risk assessment is essential for classification into high- and low-risk categories in or-

Table 1. Composition of the Rockall score [modified from 21]

Variable	Points			
	0	1	2	3
Age (years)	<60	60–79	≥80	
Shock	Pulse <100/min BP ≥100 mm Hg	Pulse ≥100/min BP ≥100 mm Hg	BP <100 mm Hg	
Comorbidities	None		Cardiac failure, ischemic heart disease, any major comorbidity	Renal or liver failure Disseminated malignancy
Diagnosis	Mallory-Weiss lesion or no lesion found	All other diagnoses	Gastrointestinal malignancy	
Stigmata of a recent hemorrhage	None or a dark spot only		Blood, nonbleeding visible vessel, spurting vessel or adherent clot	

BP, blood pressure.

der to set up further therapeutic management strategies. Several prognostic scores for pre- and postendoscopic calculations have been developed [21–24]. The Glasgow-Blatchford score (GBS) and the Rockall score are the most popular and commonly used scores [21, 22]. The GBS (range 0–23), which only consists of clinical and laboratory parameters, is superior for preendoscopic risk stratification to identify patients suitable for outpatient care. The GBS was initially developed to predict a composite of clinical intervention (transfusion, endoscopy, or surgery), rebleeding, or death, whereas the Rockall score was designed to predict mortality and rebleeding after endoscopy [21, 22, 25]. However, it has to be noted that neither of these scores are able to precisely identify individual high-risk patients, especially not before performing endoscopy. In fact, pre-endoscopic scores have an eminent role in detection of low-risk patients, who can be treated as outpatients. Therefore, 2 large comparative studies with 3,012 and 2,305 patients showed that GBS ≤1 was the optimum threshold (sensitivity: 99%; specificity: 35–0%) for the low-risk cutoff and these patients could be treated as outpatients [26, 27].

However, in addition to individual risk factors, the complete Rockall score (range 0–11) also includes endoscopic findings (Table 1) and allows prediction of mortality and the risk of rebleeding [21, 28, 29]. It has been shown that this score enables stratification of patients into low- (Rockall score ≤2), intermediate- (Rockall score 3–5), and high-risk (Rockall score ≥6) categories [28, 29]. The fact that this score also includes endoscopic findings, which additionally account for the rebleeding risk of DU, makes it more favorable when planning further surgical or interventional therapies.

Regarding recent national and international recommendations, at least one of these scores should be used in the management of bleeding ulcers [18, 19, 25, 30, 31].

Medical Management

The administration of proton pump inhibitors (PPI) has been evaluated in several studies and is recommended in guidelines for pre- and postendoscopic medical treatment [18, 19, 30–32]. A Cochrane analysis of 6 RCT including 2,223 patients found that preendoscopic administration of PPI significantly reduces high-risk stigmata of bleeding (37.2 vs. 46.5%, OR = 0.67) and the need for endoscopic intervention (8.6 vs. 11.7%, OR = 0.68), but interestingly it had no effect on rebleeding, mortality, or the need for surgery [33]. While PPI effects are well known and the therapy is well established, the application form, dosage, and therapy duration are still being discussed. Several studies have found that high-dose PPI treatment (80-mg esomeprazole bolus i.v. and continuous infusion of 8 mg/h for 72 h) reduces rebleeding, the need for surgery, and mortality following endoscopy [34–36]. Nevertheless, a Cochrane review, which included 22 RCT, could not confirm the superiority, inferiority, or equivalence of high-dose over lower-dose PPI treatment [37]. Further studies are needed to clarify the application form, dosage, and treatment duration for patients with bleeding ulcers. In the meantime, a high-dose regime seems reasonable and is actually recommended in patients with bleeding ulcers [18, 19, 25, 30, 32].

Additionally, prokinetic agents have been shown to have a positive effect on gastric emptying, and, when administered before endoscopy (usually 30–120 min), enabled better endoscopic visualization [25]. A meta-analysis including 6 RCT with a total of 558 patients showed that infusion of erythromycin significantly improved endoscopic visualization, reduced the need for second-look endoscopy, decreased the transfusion rate, and shortened the length of hospital stay [38]. However, the use of PPI and prokinetic agents should not delay urgent endoscopy in patients with active ulcer bleeding.

Endoscopy

Timing of the Initial Endoscopy

Endoscopy is the absolute gold standard for the diagnosis and therapy of bleeding DU. Localization of the exact bleeding site allows further risk stratification and endoscopic therapy in a single step. Nevertheless, the timing of endoscopy in patients with UGIB is still often discussed. Recent guidelines recommend that endoscopy be performed within 24 h after presentation of patients with upper GI bleeding [18, 19, 31]. However, it is necessary to further differentiate patients according to their risk profile and their hemodynamic situation. In patients with hemorrhagic shock endoscopy should be urgently performed after hemodynamic stabilization within 12 h [18, 19]. A prospective RCT with 325 patients was able to show that early endoscopy within 12 h significantly reduced the transfusion rate (450 vs. 666 mL; $p < 0.001$) [39]. In patients without hemorrhagic shock, early endoscopy within 24 h of the initial presentation is adequate [31]. Lau et al. [40] investigated in a recent RCT the timing of endoscopy, in particular whether urgent endoscopy improves outcomes in high-risk patients (GBS ≥ 12). They randomized 516 patients to urgent (within 6 h after gastroenterologic consultation) and early endoscopy (within 6–24 h after gastroenterologic consultation). Considering the time period from the initial presentation of the patient to gastroenterologic presentation and randomization, endoscopy was performed at a mean of 9.9 h in the urgent-endoscopy group and at a mean of 24.7 h in the early-endoscopy group. Interestingly, urgent endoscopy did not lead to a lower mortality or a reduction of further bleeding compared to the other group, although more actively bleeding ulcers and bleeding stigmata were found in the urgent group. According to the authors, this might be a result of the longer duration of acid suppression resulting in a decreased number of actively bleeding ulcers and major bleeding stigmata. So, these results suggest that endoscopy of high-risk patients can be performed within 24 h after presentation. Because patients with hypotensive shock or missing stabilization after the initial resuscitation were excluded in this RCT, these results cannot be generalized to this group. Taken together, the available evidence suggests that endoscopy within 24 h is appropriate for most patients with ulcer bleeding, assuming stable hemodynamic conditions. However, it also highlights the importance of initial patient management and resuscitation to enable adequate timing of endoscopy.

Endoscopic Risk Classification

The first key step of endoscopic bleeding management is to classify bleeding lesions in order to predict the prognosis and to exhibit a certain guidance for further thera-

Table 2. Forrest classification and the corresponding rebleeding risk without endoscopic therapy [41]

Forrest class	Endoscopic appearance	Rebleeding risk, %
Active hemorrhage		
Ia	Arterial, spurting	90
Ib	Oozing	50
Signs of recent hemorrhage		
IIa	Visible vessel	25–30
IIb	Adherent clot	10–20
IIC	Hematin-covered lesion	<10
Lesions without active bleeding		
III	Clean base ulcer	<5

peutic decisions. Therefore, Forrest et al. [41] published more than 45 years ago a classification of recent hemorrhage stigmata, which is still in routine clinical use. It still is of great importance and indispensable for further risk stratification. Table 2 summarizes the Forrest classification with the corresponding rebleeding risk. Regarding this classification and according to trials assessing rebleeding risk, Forrest Ia, Ib, and IIa lesions are independent risk factors and therefore endoscopic therapy is recommended in these lesions [18, 19, 25, 30–32]. On the other hand, Forrest IIC and III lesions have a relatively low rebleeding risk (<10% and <5%) and a low mortality (3 and 2%) [41, 42].

Endoscopic Therapy Modalities

All patients with high-risk bleeding stigmata (Forrest Ia to IIa) should undergo endoscopic therapy. Thus, endoscopic hemostasis can be obtained using injection (epinephrine and thrombin/fibrin glue), thermal (e.g., bipolar forceps and a heater probe), and mechanical (clips; Fig. 2) therapy modalities. While epinephrine (adrenaline) injection is effective for achieving bleeding control, its use as monotherapy has to be shown to be inferior in preventing ulcer rebleeding in patients with high-risk stigmata [35, 43, 44]. Therefore, it is recommended to combine epinephrine injection therapy with a second endoscopic modality to reduce rebleeding [18, 19, 25, 30, 31]. Nevertheless, primary use of epinephrine injection is of clinical advantage in patients with high-risk stigmata. Epinephrine injection therapy can slow or temporarily stop ulcer bleeding, resulting in improved visualization, allowing a second therapy modality [18]. Combination of other techniques such as clips and fibrin glue has not been shown to have any additional effect [18]. If hemostasis cannot be achieved using any endoscopic technique, the bleeding DU should be at least marked using clips in order to enable visualization of bleeding localization for further radiological interventions.

Fig. 2. Bleeding DU (Forrest IIa) with a clipped vessel.

In patients with an adherent clot on the ulcer base (Forrest IIb) endoscopic treatment is still controversially discussed because of conflicting data. When vigorous irrigation is performed, an underlying high-risk lesion (Forrest Ia–IIa) can be revealed in up to 43% of cases [45]. When clots cannot be removed by aggressive irrigation, it is still a subject of discussion whether they should be removed by more vigorous methods like cold guillotining with a snare. Two RCT showed that clot removal and consecutive endoscopic treatment of the underlying lesion was associated with less rebleeding compared to medical therapy alone [46, 47]. On the other hand, 2 meta-analyses found no differences in rebleeding rates between patients with endoscopic therapy and patients with medical therapy alone [43, 48]. Based on these inconsistent results, current recommendations suggest that either clot removal or medical therapy alone is feasible [18, 31].

Endoscopic therapy is not indicated in patients with Forrest IIc and III lesions because of the low rebleeding risk.

Current Changes in Endoscopic Treatment

Mechanical therapy modalities are effective treatment options and they are considered a standard treatment in the management of DU. In most cases “through-the-scope clips” (TTSC) are used, but these have their limitations especially with large and fibrotic ulcers. Here TTSC are difficult to apply and sometimes approximate mucosa inadequately, resulting in insufficient hemostasis or rebleeding [49]. Therefore, “over-the-scope clips” (OTSC) are increasingly used in the management of ulcer bleeding. Because of their size, their design, and their significant higher compression force, OTSC can anchor much

better in fibrotic ulcers. Schmidt et al. [50] investigated in the first multicenter RCT the outcomes of using OTSC in patients with recurrent peptic ulcer bleeding. They showed that use of OTSC resulted in a significant higher clinical success rate of 84.9% compared to 42.4% using the standard therapy (93.9% TTSC and 6.5% gold probe). The fact that 72.7% of bleeding ulcers in the OTSC group were located in the duodenum highlights the efficiency of these clips also for this anatomical location [50]. Furthermore, the multicentric FLETRock study showed that using OTSC in patients with a Rockall risk score ≥ 8 resulted in a significant reduction of rebleeding- and rebleeding-associated mortality compared to the Rockall cohort [51]. Furthermore, a recent systematic review investigated the efficiency and safety of OTSC including 58 articles comprising 1,868 patients [52]. Performing a pooled proportion analysis, this study revealed a high technical success rate of 93.0% (95% CI 90.2–95.4) using OTSC in patients with hemorrhage. Also, a high clinical success rate of 87.5% (95% CI 80.5–93.2) was demonstrated using OTSC. Taken together, these results suggest OTSC as a possible treatment of choice for patients with high-risk ulcers. Especially when rebleeding occurs, OTSC should be used in a second endoscopic treatment.

Postendoscopic Management

Right after endoscopy it is crucial to reassess the individual risk in every patient in order to identify “high-risk” patients with an increased rebleeding risk and mortality. At this point it has to be noted that an exact standardized definition of “high-risk,” especially in DU, does not exist. Based upon risk classification systems, like the Rockall score, several other factors have to be considered when determining the individual rebleeding risk. Rebleeding occurs in 8–25% of patients with nonvariceal UGIB and it still is a major problem in the management of bleeding PU. In a recent Korean prospective cohort study, 897 patients were analyzed to determine factors associated with rebleeding in patients with PUD [53]. Whereas most studies investigating this were performed in the pre-PPI era and restricted in endoscopic treatment options, that study showed a more recent view. It was shown that the presence of comorbidities, the use of multiple drugs, albumin levels, and an initial clinical presentation with hematochezia/hematemesis are associated risk factors for rebleeding.

On the other hand, several endoscopic findings are known which are associated with a poor outcome [54, 18]. Especially, ulcers on the posterior wall of the duodenal bulb are associated with a higher rebleeding risk. Table 3 gives an overview of the most significant risk factors for rebleeding.

Table 3. Clinical and endoscopic risk factors for rebleeding [54]

Risk factors	
Clinical	Endoscopic
Hemodynamic instability	Ulcer size >2 cm
Low hemoglobin level	Ulcer location (duodenal posterior wall)
Comorbidities	Large size nonbleeding vessel

Very often routine second-look endoscopies are performed. These are primarily defined as a planned endoscopic assessment within 24 h after a primarily successful endoscopic treatment regardless of the rebleeding risk. This approach is still discussed but should no longer be a part of routine practice. Interestingly, a meta-analysis that investigated the role of routine second-look endoscopy found a significant reduction in rebleeding and the need for surgery, but not in mortality [55]. However, it has to be noted that this analysis included only 1 study, which used high-dose intravenous PPI, and exactly that study found no benefit of routine second-look endoscopy; it did report protective effects only for high-risk patients. Thus, routine second-look endoscopy is not recommended in unselected patients, but it can be an option in patients with a high-risk constellation or those with unsatisfactory hemostasis at the initial endoscopy [18].

Management of Persistent DU Bleeding

Alternative treatment strategies have to be chosen when endoscopy fails and bleeding persists or reoccurs. In general, 2 treatment options are currently available, i.e., surgery and transcatheter arterial embolization (TAE; Fig. 1). Both treatment options have pros and cons, and the individual clinical presentation and local factors such as the availability of an experienced radiologist or surgeon determine further therapeutic steps. Additionally, patients with high-risk DU are also usually older and have more comorbidities, which has to be taken into account when choosing between surgery and TAE [56].

Surgery

Historically, surgery has been the first choice of treatment after a failed endoscopy. Regarding bleeding ulcers, the following 2 indications for surgery still exist: first, when endoscopic therapy is unsuccessful and bleeding persists primarily, and second, when bleeding reoccurs after a successful reendoscopy. In fact, about 2.3–10% of patients need surgery because of a failed endoscopic treatment [57–59]. Various surgical techniques exist, especial-

ly for treating bleeding DU, ranging from local approaches (ulcers suture with or without extraluminal ligation of the GDA) to gastroduodenal resections (distal gastrectomy with partial duodenectomy). Nevertheless, surgery is still associated with high morbidity rates (~50%) and high mortality rates (ranging from 18 to 40%) [60–62]. A meta-analysis including 6 studies showed a high pooled frequency of surgery-related complications of 46%, ranging from pneumonia, postoperative abscess, and duodenal stump leakage to multiorgan failure [63]. However, these results have to be reflected upon considering the facts that patients are often elderly, have significant comorbidities, have received a blood transfusion, have suffered hypotension, and commonly have a complicated high-risk DU. Thus, endoscopy and conservative therapy automatically select a subgroup of patients who have a higher risk of complications. Very often, these patients undergo several attempts of endoscopic treatment with temporary bleeding control, resulting in a much higher risk and a worse prognosis. Two studies investigated early elective operation in patients and found that it was less likely associated with rebleeding but did not affect mortality [60, 64]. However, patients who underwent surgery had a significantly higher complication rate and endoscopic retreatment controlled rebleeding in about three quarters of the patients [60]. Interestingly, Lau et al. [60] found that an ulcer size >2 cm and hypotension at the time of rebleeding were independent risk factors for unsuccessful endoscopic retreatment. Therefore, surgery seems reasonable in patients with a high risk of rebleeding, but it requires careful surgical judgement due to the high risk of the patients.

Transcatheter Arterial Embolization

Forty years ago, Rösch et al. [65] first described the use of angiography and TAE for controlling acute gastrointestinal bleeding. TAE is a serious alternative to surgery and even the first treatment choice after failed endoscopic therapy.

Usually, the endoscopist has already identified the bleeding localization, attempted local bleeding control, and ideally positioned a clip at the bleeding DU. Also, when bleeding control cannot be reached, marking the bleeding site with a clip is an important step. It makes it easier for the interventional radiologist to identify bleeding localization for embolization because active extravasation is only found in up to 61% of cases [56]. In these cases, where no active bleeding can be detected at the initial angiography, a so-called “empiric” or “blind” embolization of the targeted vascular bed has to be performed. To ensure therapeutic success of empiric embolization, it is crucial to determine and describe the exact bleeding localization endoscopically besides clip marking. This is especially essential for the posterior wall of the duodenal

Fig. 3. Empiric TAE after endoscopy. **A** Arteriogram with the bleeding site marked with a clip. **B** Complete embolization of the GDA with coils.

bulb, because the GDA with its branches is mostly related to the bleeding site. Therefore, empiric embolization is safe and effective irrespectively of extravasation, when the bleeding site is endoscopically identified [10, 66–74]. In general, technical and clinical success rates of 90–100% and 44–93% for TAE in patients with refractory DU bleeding have been reported and indicate its efficiency [10, 69, 71, 72, 74–76]. The actual coaxial catheter systems and the variety of embolic agents (e.g., polyvinyl alcohol, gelatine sponge, N-butyl cyanoacrylate, and coils) allow a superselective embolization of the targeted vessel. The complication rate of TAE is relatively low and a meta-analysis including 6 studies reported a pooled frequency of TAE-related complications of 4% [63]. These included ischemic pancreatitis, renal impairment, and misplacement of coils. However, in general, ischemic complications are very rare due to the very rich collateral blood supply of the duodenum [77].

On the other hand, the complex anatomy of the GDA is one reason for the high rebleeding rate of 8–55% reported in some studies [75, 10, 66–71, 75, 76]. For that reason, a detailed anatomic knowledge of the GDA is necessary in order to embolize the vessel to the right extent and with a suitable technique. The GDA has dual blood supply from the common hepatic artery and the superior mesenteric artery. While it most commonly arises from the common hepatic artery, and gives rise to the supraduodenal and posterior pancreaticoduodenal artery, the GDA splits into the right gastroepiploic and the anterior pancreaticoduodenal artery. Together with the inferior pancreaticoduodenal arteries, which arise from the superior mesenteric artery, functional anastomoses are formed. Regarding this anatomical specialty, embolization of the GDA solely at its proximal part will inevitably result in reperfusion of the distal GDA via the superior mesenteric artery. For that reason, a complete embolization of the GDA, starting from the distal portion and con-

tinuing to the origin, should be performed to reduce rebleeding rates (Fig. 3). Additionally, selective angiography of the superior mesenteric artery should be performed at the end of every embolization of the GDA to exclude collateral blood supply to the bleeding site [56].

Surgery versus TAE

Initially TAE was only used in poor surgical candidates, while surgery was the primary treatment option in patients with persisting bleeding. However, TAE has widely spread and it is currently used in clinical practice. It has been demonstrated in several case studies that it is a safe alternative also in patients unfit for surgery. However, when analyzing rebleeding rates it has been shown that TAE might be associated with an increased rebleeding rate compared to surgery. A recent meta-analysis of Kyaw et al. [63] including 6 studies with a total of 423 patients, which compared TAE and surgery for the management of recurrent nonvariceal UGIB, confirmed a significant higher rebleeding risk with TAE compared to surgery (RR = 1.82; 95% CI 1.23–2.67). However, despite this higher rebleeding rate, no difference in mortality between these 2 modalities could be detected. It has to be noted that patients treated with TAE were also older and had a poorer health status in this meta-analysis, which might additionally explain this missing difference in mortality. This study also showed that rebleeding in the TAE cohort varied considerably between the included studies (15–40%). This might be related to the application of different embolic agents and techniques. For example, resorbable embolic agents like gelatin sponge are like to be linked with a higher risk of rebleeding. That might have influence the results of this study. Additionally, a complete embolization of the bleeding vessel, e.g., the GDA, is essential and superior to central embolization of a bleeding site alone. Unfortunately, most of the reported studies do not mention embolic agents or embolization

techniques [63]. While the higher risk of rebleeding was confirmed in a recent population-based cohort study including 282 patients, TAE was still associated with a better prognosis, a shorter length of hospital stay (9 vs. 18 days; $p < 0.0001$), and a decreased risk of complications (8 vs. 32.2%; $p < 0.0001$) compared to surgery [73]. Considering these results and the fact that surgery is associated with a significantly higher morbidity, the use of TAE is increasingly proposed as first treatment choice [72, 78, 79].

Beside these differences, further therapeutic steps in patients with unsuccessful endoscopy should be decided upon in a multidisciplinary manner (endoscopist, surgeon, and interventional radiologist) based on the individual patient condition (age and comorbidity) and bleeding lesion. In this context it should also be noted that ulcer surgery, especially in bleeding situations, has declined over in the last decades and therefore not every surgeon might be equally experienced. On the other hand, TAE and adequate embolization of the GDA requires an experienced interventional radiologist. So, these institutional conditions have to be considered when choosing further therapeutic modalities. However, according to all these case series and studies, evidence suggests choosing TAE prior to surgery, especially in high-risk patients.

Prophylactic TAE

A more recent approach is the concept of prophylactic TAE in patients with high-risk bleeding ulcers after successful endoscopic hemostasis. This concept is thought to reduce the rebleeding rate and mortality in selected patients. In 2014, Laursen et al. [80] published the first RCT according to this concept of prophylactic embolization. Patients with high-risk peptic ulcers (Forrest Ia to IIb) were randomized after endoscopic hemostasis to prophylactic TAE or conservative treatment. Unfortunately, that study was underpowered, so they could only show that prophylactic TAE can be safely performed without detecting a difference in endpoint variables. Subsequently, we investigated, in an own retrospective study including 117 patients with bleeding DU, the concept of prophylactic TAE ($n = 55$). Prophylactic TAE was implemented in our hospital in 2008 and is regularly used successfully in high-risk situations. Patient selection for TAE was performed with respect to endoscopic findings (Forrest Ia to IIc, posterior duodenal bulb, and ulcer size), the Rockall score, and individual factors (comorbidities, anticoagulants, and hemodynamic instability). In this study we could show for the first time that establishing prophylactic TAE in high-risk DU is safe and effective, resulting in a low surgery rate ($n = 1$; 0.9%) and a low bleeding-associated mortality of 4.3% [72]. Additionally, Kaminskis et al. [81] could also show in a following study including 399

patients with bleeding high-risk ulcers that prophylactic TAE resulted in a lower rebleeding rate (3.4 vs. 16.2%; $p = 0.005$) and a low rate of surgical intervention compared to the standard treatment. The main criteria for prophylactic TAE in this study were ulcer an classification of Forrest Ia to IIb, a Rockall score ≥ 5 , and an individual high-risk profile (age and comorbidities).

On the other hand, a recent published RCT involving 241 patients compared prophylactic TAE after endoscopic hemostasis with standard treatment [82]. Patients were randomized, when at least 1 of the following criteria was present: ulcer size ≥ 20 mm, spurting bleeding, hypotensive shock, and hemoglobin < 9 g/dL. The authors could not find a benefit using prophylactic TAE in that study. Interestingly, rebleeding was only reduced in patients with an ulcer size ≥ 15 mm. Nevertheless, this study shows that risk stratification is essential and has to include multiple factors.

At the moment there is not sufficient data to recommend prophylactic TAE in recent guidelines. Furthermore, specific selection criteria involving multiple risk factors have to be further investigated in order to select suitable high-risk patients for prophylactic TAE. However, especially in duodenal high-risk ulcers (posterior duodenal bulb) with a corresponding patient risk profile and/or suboptimal endoscopic hemostasis, prophylactic TAE might be an essential therapy modality.

Conclusion

Therapeutic management of high-risk DU is a multidisciplinary challenge and involves several disciplines. There is no doubt that endoscopy is the gold standard and the treatment of choice. Nevertheless, persistence and rebleeding are serious complications in patients with bleeding DU. Therefore, risk classification and identification of these patients is elementary for further management. Additionally, patients with high-risk DU usually exhibit several comorbidities, receive anticoagulants, and are often in worse condition, and thus the choice of repeat endoscopy, surgery, or TAE has to be made on an individual basis considering the institutional resources. Nevertheless, the treatment strategy should be: identify high-risk patients, avoid rebleeding, and promptly decide on a further treatment option based on local resources.

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