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Turn over the new leaf of the treatment in peptic ulcer bleeding: a review of the literature

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***Abstract*:** Peptic ulcer bleeding is the most common cause of upper gastrointestinal bleeding, which has a high mortality risk. The standard therapy for acute peptic ulcer bleeding combines medication administration and endoscopic therapies. Both pharmacologic and endoscopic therapies have developed continuously in the past few decades. Proton pump inhibitors (PPIs) already reached a high efficacy in ulcer healing and have been widely used in the past few decades. Endoscopic hemostasis, which includes local epinephrine injection, heater probe coagulation, use of hemostatic clips, and/or band ligation, is highly effective with an overall hemostatic success rate of 85%–90%. However, 10%–20% of patients could not be cured by the current standard combination treatment. Recurrent ulcer bleeding, despite an initial successful hemostasis, is also a big problem for longer hospitalization stays, higher mortality, and higher complication rates, especially for malignant ulcer bleeding. How to manage all types of peptic ulcer bleeding and how to prevent early recurrent peptic ulcer bleeding remain unresolved clinical problems. Recently, several novel medications and endoscopic methods have been developed. Potassium competitive acid blockers have shown a stronger and longer acid suppression than PPI. Hemostatic powder spray and hemostatic gel emulsion are novel hemostatic weapons with emerging evidence, which are potential missing pieces of the puzzle. This literature review will go through the development of endoscopic hemostasis to the prospects of novel endoscopic treatments.

Keywords: endoscopic hemostasis, hemostatic gel emulsion, hemostatic powder spray, P-CAB, peptic ulcer bleeding

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Introduction

A peptic ulcer is a mucosal break with a size over 5 mm that forms in the lining of the stomach or the duodenum. Many kinds of etiologies can result in peptic ulcer disease. *Helicobacter pylori* (Hp) infection and non-steroidal anti-inflammatory drugs (NSAIDs) are the two major causes of peptic ulcers.[1] Other uncommon etiologies for peptic ulcers are named Hp-negative, NSAID-negative ulcers, including gastrinoma (Zollinger–Ellison syndrome), gastric malignancy (adenocarcinoma and lymphoma), Crohn disease, eosinophilic gastroenteritis, viral infections, Behcet disease, acute stress, and mucosal ischemia.[2]

Gastric acid, bicarbonate, and digestive enzymes compose the gastric environment with a dynamic pH value between 1.5 and 3. In normal conditions, protective mechanisms of the stomach can protect and repair the gastric mucosa. When an imbalance between gastric acid and mucosal protection occurs, such as gastric acid hypersecretion and impaired duodenal bicarbonate secretion, it may result in peptic ulcer disease. Hp infection can disrupt the protective mucous layer, causing gastritis and impair the mucosa healing.[3] Hp-induced antral inflammation can also increase basal and stimulated gastric acid secretion.[4] NSAIDs inhibit mucosal prostaglandin synthesis, which can reduce the mucosa blood flow, the

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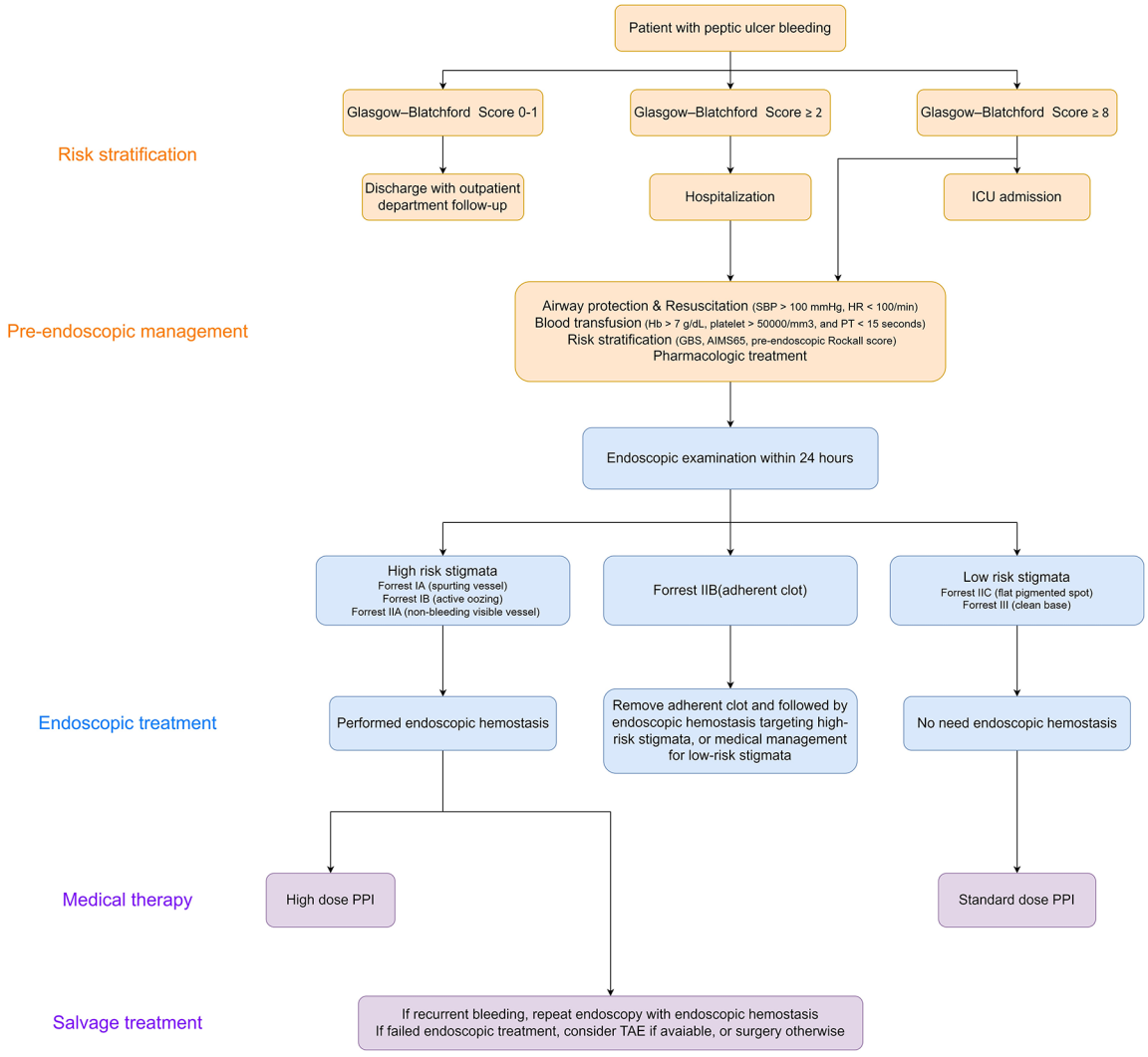

Figure 1. Management flowchart for peptic ulcer bleeding.

integrity of the mucosal barrier, and the amount of bicarbonate.[5]

Common symptoms of peptic ulcers include epigastric pain, bloating, nausea, vomiting, and in severe cases, bleeding or perforation of the stomach or duodenum.[1,6] The most common complication of peptic ulcers in emergency departments is bleeding, approximately 100–170 per 100,000 worldwide. Peptic ulcer bleeding is a serious medical condition causing hematemesis, melena (tarry stool), or hematochezia. Patients without timely treatment can progress into anemia, hypovolemic shock, multiorgan failure, or even death. The mortality rate of peptic ulcer bleeding is approximately 5%–12%.[7,8] Therefore, clinicians have been dedicated to developing the most effective treatment for peptic ulcer bleeding for decades.

Current treatment for peptic ulcer bleeding

A standardized assessment and timely treatment are necessary for patients with bleeding peptic ulcers (Figure 1). The initial step is stabilizing the patient's hemodynamic status and airway patency. The treatment goal of fluid resuscitation is to keep systolic blood pressure over 100 mmHg and pulse lower than 100/min by intravenous crystalloid fluid resuscitation. Packed RBC, platelets, and fresh frozen plasma transfusion are needed to keep the hemoglobin level higher than 7 g/dL, platelet counts over 50,000/

Risk stratification	Predictor	Score	Interpretation
Glasgow–Blatchford Bleeding Score	Urgency of endoscopic therapy	0	Low risk
		> 0	High risk → need intervention
		≤ 1	Discharge with outpatient follow-up
		≥ 8	ICU admission
AIMS65	In-hospital mortality	0	0.3%
		1	1.2%
		2	5.3%
		3	10.3%
		4	16.5%
		5	24.5%
Pre-endoscopic Rockall score	Mortality risk	0	0.2%
		1	2.4%
		2	5.6%
		3	11%
		4	24.6%
		5	39.6%
		6	48.9%
		7	50%

Figure 2. Risk assessment score interpretation for peptic ulcer before endoscopy.

mm^3, and prothrombin time international normalized ratio (PT-INR) less than 15 s.

Several risk score assessments have been designed to assist with the risk stratification for peptic ulcer bleeding patients (Figure 2). Glasgow–Blatchford bleeding score aimed to identify the urgency of endoscopic therapy by using the patient's blood test, blood pressure, past history, and clinical presentations.[9] A score >0 is in need of medication and endoscopic intervention, while a score over 8 points is indicated for ICU admission. The AIMS65 scale has been proven to predict in-hospital mortality and length of hospitalization by using the patient's blood test, blood pressure, and clinical presentations.[10] On the other hand, the pre-endoscopic Rockall score is a useful prognostic indicator to identify mortality risk by using vital signs and past history.[11]

After risk assessments, patients with bleeding peptic ulcers should receive pharmacologic treatment and endoscopic examination within 24 h. The current guideline suggests intravenous proton pump inhibitor (PPI) as the first choice for gastric acid suppression, and the dose and duration depend on the endoscopic findings. The endoscopic finding of bleeding peptic ulcers can be classified by Forrest classification (Figure 3), which can identify high or low risk for rebleeding and mortality.[12,13] Forrest IA (spurting vessel), IB (active oozing), IIA (non-bleeding visible vessel), and IIB (adherent clots) are defined as major stigmata of recent hemorrhage (SRH), indicating a higher rebleeding and mortality risk in need of appropriate endoscopic treatment.[12] Forrest IIC (flat red spot) is defined as minor SRH with a lower risk, and Forrest III (clean base) is without recent SRH.[14] In combination with the clinical presentation and endoscopic findings, the complete Rockall score predicts the rebleeding and mortality risk.[15,16] A complete Rockall score of 0–1 was low risk, 2–4 was intermediate risk, and ⩾5 was defined as a high risk.[16]

Pharmacologic treatment

Peptic ulcer healing is a reconstruction process of mucosa through the formation of granulation tissue.[17] Granulation tissue formation takes place approximately 72 h through the formation of the ulcer base, blood vessel, and re-establishment of glandular architecture after the ulcer occurs.[18] To ensure the appropriate environment for ulcer healing, pharmacologic treatment of peptic ulcers includes three aspects—acid suppression, mucosa protection, and Hp eradication.[19]

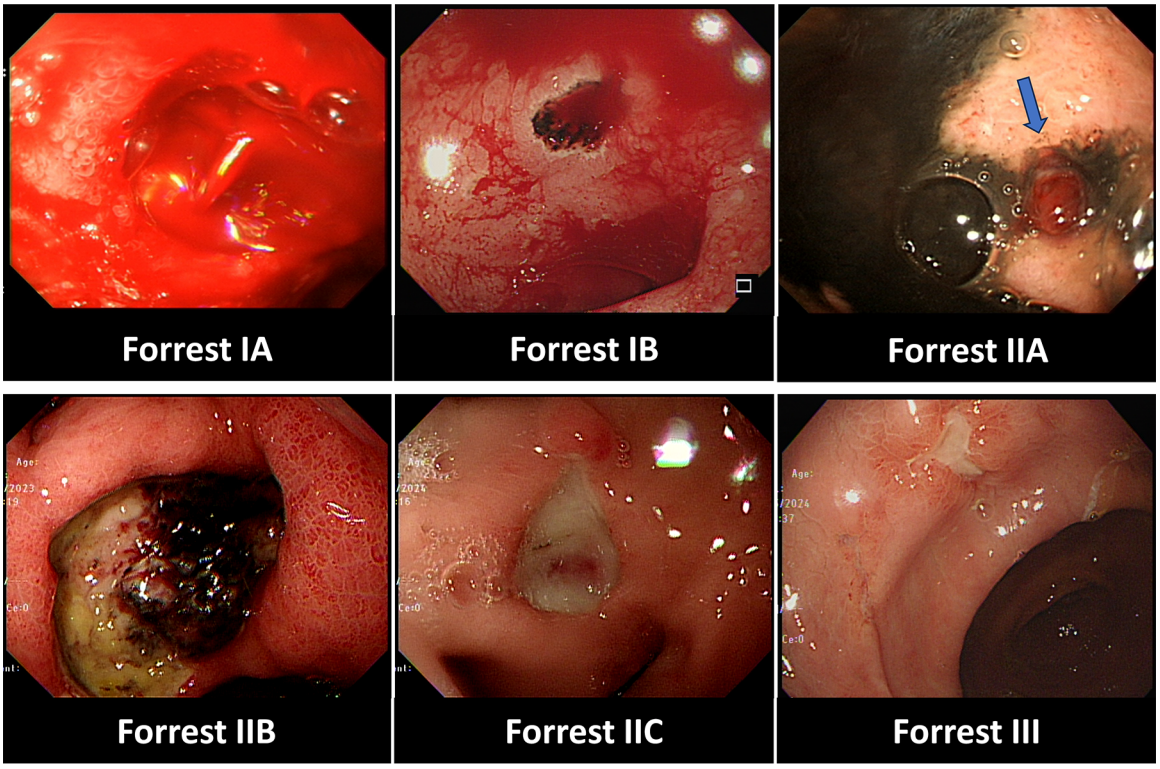

Figure 3. Forrest classification of peptic ulcer.

PPI and histamine (H2) receptor antagonists. Gastric acid impairs clot formation, induces platelet disaggregation, and facilitates clot lysis.[20,21] Acid suppression to keep intragastric pH > 3 over 20 h is the mainstay of a peptic ulcer treatment.[22] PPIs can inhibit gastric acid secretion by blocking the H+/K+ ATPase enzyme activity by covalently binding to its sulfhydryl group of parietal cells in the stomach.[23] PPIs are prodrugs requiring gastric acid secretion to be converted to the active form.[24] After the conversion into active sulfenamide or sulfenic acid, PPIs can maintain intragastric pH > 4 for approximately 20 h per day.[25] In contrast, H2 receptor antagonists can only maintain intragastric pH > 4 for 8 h, and tachyphylaxis may occur within 3–5 days of regular use.[26]

In 2015, United States Food and Drug Administration (FDA) approved six types of PPIs—omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole. For peptic ulcer-related active bleeding, intravenous esomeprazole and pantoprazole are suggested.[27] Before endoscopic evaluation, administration of intravenous PPI can reduce the proportion of participants with SRH and the requirement for endoscopic therapy.[28] After standard endoscopic treatment, bolus (80 mg) with continuous infusion of high-dose (8 mg/hr) esomeprazole or pantoprazole for 72 h is suggested for patients with major SRH to reduce the rate of rebleeding, in need of surgery, and mortality.[29,30] For patients with a minor SRH peptic ulcer or a clean-based ulcer, a standard dose of oral PPI is sufficient for ulcer healing.[31]

Potassium-competitive acid blocker. Potassium-competitive acid blocker (P-CAB) inhibits H+/K+ ATPase in gastric parietal cells.[32] Different from oral-form PPIs, P-CABs are not degraded by gastric acid, so P-CABs do not require enteric coating before absorption. Besides, P-CABs are active drugs, not prodrugs as PPIs. In this situation, P-CABs can reach a near-maximum inhibitory effect from the first dose and remain effective for 24 h, while oral-form PPIs require 3–5 days for maximal acid inhibition.[33,34] P-CABs have potential superior effects over oral PPIs due to stronger acid suppression, stability in acidic environments, faster drug onset, and longer half-life.[35]

Vonoprazan, one of the P-CABs, has been proven to be non-inferior to oral PPIs in erosive esophagitis,[36] Hp eradication,[37] recurrent peptic ulcer prevention,[38,39] and ulcer treatment.[40] Due to stronger acid suppression and faster drug onset, P-CABs have potential benefits in bleeding peptic ulcers.[35] For bleeding peptic ulcers, a recent multicenter randomized clinical trial revealed a non-inferior effect of oral-form vonoprazan to intravenous high-dose PPI in preventing 30-day rebleeding after a successful endoscopic hemostasis.[41] It can be expected that P-CABs will play more important roles in the treatment of peptic ulcer bleeding in the future.

Tranexamic acid. Tranexamic acid (TXA) is an antifibrinolytic medication that functions by inhibiting fibrin degradation through binding to tissue plasminogen, thus impeding blood clot breakdown and diminishing bleeding.[42] Numerous studies have demonstrated its efficacy in reducing blood loss and transfusion requirements in surgical bleeding scenarios.[43–45]

However, its application in gastrointestinal (GI) bleeding remains controversial. TXA may be effective in reducing GI-bleeding-related mortality, but its hemostatic ability is inconsistent.[46] A multicenter study—Hemorrhage Alleviation with Tranexamic Acid–Intestinal System (HALT-IT) trial—concluded that intravenous TXA failed to prevent GI-bleeding-related deaths among 12,009 patients.[47]

The antifibrinolytic properties of TXA are at the bleeding site.[48,49] In contrast to systemic application, local administration is anticipated to yield superior efficacy. A recent clinical trial demonstrated a lower treatment failure rate and longer freedom from 28-day rebleeding spraying topical TXA after endoscopic hemostasis on a bleeding peptic ulcer.[50]

Sucralfate. Sucralfate, a basic aluminum salt of sucrose octasulfate, can increase mucus secretion, mucosal blood flow, and local prostaglandin production.[51,52] In the presence of acid, the sucralfate tablet dissolves into an aluminum salt and sucrose sulfate to bind to exposed proteins on damaged cells and create a protective layer to shield the GI mucosa.[53] Sucralfate also binds to growth factors and thus promotes angiogenesis and mucosal healing.[54] Therefore, sucralfate has been used in the treatment of GI ulcers.[55,56]

For preventing peptic ulcer bleeding, sucralfate can prevent stress ulcers in critical patients in ICU.[57] Applying sucralfate to the stomach through a nasogastric tube (2 g every 8 h) can reduce the formation of peptic ulcers.[58] In vitro, sucralfate can protect the blood clot from gastric acid lysis.[59] However, for active peptic ulcer bleeding, sucralfate has shown no impact on hemostasis.[60] This may be because sucralfate cannot alter gastric acid secretion or buffer acid, and it only has a local effect to protect the blood clot and the ulcer by direct contact.[61] Oral intake of the tablet does not guarantee the contact duration between sucralfate and the peptic ulcer, so the effect on the bleeding peptic ulcer is not evident. Otherwise, if sucralfate can be applied precisely to the bleeding ulcer site through endoscopic assistance, the hemostatic effect of this drug may be re-evaluated.

Misoprostol. Misoprostol, a synthetic prostaglandin E1 (PGE1), can directly stimulate PGE1 receptors on parietal cells in the stomach to inhibit gastric acid.[62,63] It can also induce mucus and bicarbonate secretion to improve blood flow and enhance mucosal healing.[64,65] Misoprostol has a similar effect with PPIs for NSAID-related ulcers.[66] FDA has approved misoprostol for the prevention and treatment of NSAID-induced peptic ulcers.[64] However, abdominal pain and diarrhea appear to be a prominent adverse effect of misoprostol, so the tolerance was inferior to PPIs.[66]

For GI bleeding, clinical trials demonstrated that misoprostol can reduce blood loss and promote the healing of bleeding small bowel ulcers among aspirin users.[67,68] For hemostasis, misoprostol can promote the constriction of blood vessels and reduce blood loss in surgery and labor.[69,70] However, due to the higher adverse effect frequency, no large-scale study has evaluated the hemostatic effect of misoprostol on peptic ulcer bleeding against PPIs.[71] Current guidelines for peptic ulcer bleeding do not identify the role of misoprostol. However, based on acid-suppression and mucosa-protection effect, it is believed to be beneficial during combination therapy for refractory peptic ulcers.[72]

Endoscopic treatment

Endoscopic hemostasis is the primary treatment to stop bleeding for bleeding peptic ulcers.

Without adequate endoscopic treatment, peptic ulcers with a spurting vessel (Forrest IA, 100%), active oozing (Forrest IB, 30%), non-bleeding visible vessel (Forrest IIA, 50%), and adherent clots (Forrest IIB, 30%) are generally with high risk (>30%) for recurrent bleeding.[73] After adequate combination therapy with PPI and endoscopic hemostasis, the recurrent bleeding rates can be reduced to 5%–20%.[74] On the other hand, ulcers with a clean base (Forrest III) or a flat pigmented spot (Forrest IIC) are at low risk of recurrent bleeding (<10%), and endoscopic hemostasis is not required. Endoscopic hemostatic therapy includes injection therapy (epinephrine, ethanol, and histoacryl), thermal coagulation, argon plasma coagulation (APC), hemostatic clips, and combination therapy, chosen based on the bleeding lesion's characteristics and the operator's judgment.

Injection therapy. The main method of injection therapy is diluted epinephrine, typically mixed with normal saline at ratios of 1:10,000 or 1:20,000 and injected in amounts ranging from 0.5 to 2.0 mL in four quadrants within 3 mm of the bleeding site. This mixture is chosen for its ability to induce local tamponade and vasoconstriction effects. Epinephrine injection is advantageous because it effectively slows down bleeding temporarily, especially during active hemorrhage in endoscopic procedures. This temporary slowdown helps improve visibility, facilitating the easier performance of afterward endoscopic interventions. Injection therapy alone has a higher risk of recurrent bleeding than other standard treatments, such as thermal coagulation and hemostatic clips.[75] Therefore, injection therapy alone is not an adequate endoscopic treatment. Combination therapy with epinephrine injection and another endoscopic therapy reduces the risk of recurrent bleeding after the initial treatment, which is the current standard endoscopic treatment.[75,76]

Pure ethanol is another effective injection therapy to control bleeding from peptic ulcers. Pure ethanol injection causes blood vessel constriction, sclerosis, and local thrombosis, promoting blood clot formation and hemostasis.[77] Ethanol injection revealed a prominent hemostatic effect as thermal therapy and hemostatic clips.[77–79] Aliquots of 0.1–0.2 mL of absolute ethanol were repeatedly injected, with at least two injections per quadrant, 1–3 mm from the bleeding point of the vessel. However, pure ethanol can lead to local dehydration, sclerosis, tissue necrosis, and even perforation.[80,81] The appropriate volume of ethanol is not easy to handle; less than 1 mL may avoid ulcer perforation,[82] while 1–2 mL may be needed to stop a spurting bleeder.[83] Animal experiments have shown that injecting more than 2 mL can cause severe tissue injury.[84] Therefore, the total volume per session should be limited to 2 mL for safety. Due to possible severe adverse effects, pure ethanol injection is not often applied in current endoscopic treatment.

N-butyl-2-cyanoacrylate (Histoacryl) is a liquid tissue adhesive agent, which turns into a solid material when it touches blood.[85] Cyanoacrylates quickly block bleeding vessels and have been the standard therapy for variceal bleeding. For peptic ulcer bleeding, Histoacryl injection showed a similar effect to hypertonic saline–epinephrine injection in stopping bleeding, and with an even lower rebleeding rate for active arterial bleeding.[85] However, it can cause serious issues like thromboembolism, tissue damage, or perforation.[86,87] Because of these rare but severe risks, it is recommended to use Histoacryl as a last resort before considering surgery for peptic ulcer bleeding treatment.[85]

In current endoscopic practice guidelines, the role of injection therapy is more likely a bridging therapy, especially for bleeding ulcers with spurting vessels.[75] With the rapid but short effect of tamponade by injection, the bleeding can be stopped temporarily and the endoscopic view can be clearer for the application of more reliable and endurable therapies, such as thermal and mechanical therapies.

Thermal therapy. Thermal coagulation was the first endoscopic treatment. When the temperature reaches 60°C, the protein coagulates and thus causes thermal contraction of the bleeding vessels and tissue.[88] Thermal therapies are divided into contact and non-contact modalities.[89]

Contact devices like heater probes, bipolar electrocoagulation, and soft monopolar electrocoagulation use pressure from the probe tip directly on the bleeding site, along with heat or electricity, to stop bleeding.[89] Thermal contact devices can effectively reduce recurrent bleeding and mortality rates.[29,90] Besides, combined thermal therapy with injection therapy is superior to thermal

coagulation alone in reducing rebleeding risk.[91] However, tissue vaporizes when the temperature reaches 100°C, so a higher temperature may result in extensive tissue destruction, deeper ulceration, and even perforation.[88] For patients with deep and huge ulcers, applying high temperatures to vessel walls may lead to perforation.[88] Hence, the current guideline suggests to use of the large 3.2-mm probe with firm pressure for 8–10 s.[75]

Monopolar hemostatic forceps with soft coagulation (MHFSC), a relatively new contact thermal device, has been widely used in the treatment of bleeding vessels during endoscopic submucosal dissection (ESD).[92] MHFSC works at a lower voltage (maximum of 200 V), so it is associated with a lower risk of perforation because of the reduced coagulation effect at the deep tissue level.[93] MHFSC has been proven to be effective for initial hemostasis and preventing rebleeding.[92–94]

APC is a non-contact thermal device that delivers a jet of ionized gas to the bleeding lesion.[95] Argon gas is emitted and then ionized by an electrical current that results in the coagulation of the lesion, which stops the bleeding.[96] It is commonly used for superficial vascular issues like angiodysplasia and gastric antral vascular ectasia.[97] APC application after water injection is better at preventing rebleeding from peptic ulcers than water injection alone.[96] However, while the absence of direct contact is beneficial for small superficial vessels, this method might not work as well for larger vessels.[97,98] In this situation, APC is only conditionally recommended for peptic ulcer bleeding in current guidelines.[75]

Mechanical therapies. Mechanical therapies include band ligation and clipping, providing a simple and direct local tamponade of bleeding ulcers and vessels to achieve hemostasis. Band ligation is a principle where pliable tissue is drawn into a cylindrical chamber attached to the end of an endoscope, followed by the release of an elastic band to constrict both the tissue and the vessel beneath it.[99] This method is commonly employed for variceal bleeding. Additionally, for patients with non-variceal upper GI bleeding, band ligation offers a safe and effective means of achieving hemostasis.[100,101] It has proven to be an effective and safe treatment for peptic ulcer bleeding and can serve as a salvage therapy for difficult cases unresponsive to injection therapy.[102,103] Combining band ligation with epinephrine injection has also shown superior hemostatic efficacy over epinephrine injection alone for bleeding peptic ulcers.[104] However, its efficacy is limited in cases of large ulcers with hard, fibrotic bases, which are difficult to suction into the endoscopic device before applying the elastic band.[105] Therefore, endoscopic band ligation presents itself as an alternative treatment option for small peptic ulcer bleeding.

Clipping method includes through-the-scope clip (TTSC) and over-the-scope clip (OTSC). TTSCs are metal clips that can pass through the working channel of endoscopy without the need for endoscopy withdrawal. TTSCs have been widely used for hemostasis, perforation closure, and endoscopic marking since the 1990s.[106,107] Novel TTSCs have emerged in recent years with different rotatability, open angles, tensile strength, and closure strength.[106]

For bleeding peptic ulcers, single-use of TTSC has shown a lower recurrent bleeding rate than injection therapy alone.[108] Similarly, combining TTSC with injection therapy has a lower rebleeding rate than injection therapy alone.[104,109] These results indicate that a longer and stabler direct tamponade at the bleeding vessel is the mainstay of hemostasis.[108] Although the combination therapy of TTSC and injection showed similar hemostatic efficacy to TTSC alone, the endoscopic view may be clearer after the bleeding stops by injection.[91] The hemostatic efficacy was also similar between TTSC and thermal therapy.[91] However, TTSC requires accuracy and experience, and it can be challenging to apply in specific areas (e.g. proximal lesser curvature of the stomach, posterior wall, and junction of the first and second portion of the duodenum) and with fibrotic ulcers.[110] Thermal therapy can be more accessible among those specific areas.

Different from TTSCs, endoscopy withdrawal is needed for the OTSC installation. The OTSC is shaped like a "bear claw," and the sizes (11, 12, and 14 mm) and depths (3 and 6 mm) are larger than traditional TTSCs.[111] In this situation, OTSC has a greater area captured and greater compression force than TTSCs.[112] OTSC was originally designed for the closure of GI perforations or leaks, owing to its capability to grasp a larger volume of tissue with increased compression force.[113] The strong grasp of OTSC expanded

its application to hemostasis among GI bleeding.[114] For patients with recurrent peptic ulcer bleeding, OTSC has a lower rebleeding rate than combination therapy of TTSC and injection.[115] For refractory peptic ulcer bleeding, OTSC is an effective and safe rescue therapy with a rescue rate of approximately 80%.[112,116] A recent clinical trial even proved a superior initial hemostatic rate and a lower rebleeding rate of OTSC over TTSC among first-line therapy for bleeding peptic ulcers.[117] However, another clinical trial with large peptic ulcers (size $\geq$ 1.5 cm) showed routine employing OTSCs as the primary hemostatic measure did not demonstrate a significant decrease in 30-day rebleeding compared to standard endoscopic therapy.[118] Additionally, OTSC migrated into the gastric wall, and leaking out to the third space can happen.[119] Based on current evidence, OTSC is recommended as a rescue therapy for recurrent and refractory peptic ulcer bleeding.

Challenging ulcer bleeding and salvage treatments

Despite advancements in endoscopic and pharmacological therapies, still a minority of patients (8%–15%) experience refractory peptic ulcer bleeding.[120] Predictors of rebleeding include initial hemodynamic instability, low hemoglobin levels upon presentation, greater blood transfusion requirements, high-risk endoscopic stigmata, large ulcer size, and specific ulcer locations like posterior duodenal or high lesser gastric curvature ulcers.[121,122] For patients with peptic ulcers who experience recurrent bleeding despite initial endoscopic treatment, a second-look endoscopy has shown long-term bleeding control with reduced complications, no increased mortality risk, and lower costs compared to surgery.[123] Therefore, guidelines recommend a second-look endoscopy in such cases.[75,124]

Malignancy-related ulcer bleeding is another challenge to manage. Due to local vessel invasion and friable neovascularization of tumors, malignant ulcers can rebleed even after initial hemostasis was achieved.[125] Although surgery and endoscopic resection can remove the tumor, not all patients are appropriate candidates. Standard combination therapy with injection and thermal or mechanical treatment can reach 80%–90% initial hemostasis.[126] However, the overall rebleeding rate of malignant ulcers is 40%, and the rebleeding rate within 30 days is 30%.[126] Until now, there is no strongly recommended therapy for malignant bleeding in treatment guidelines.[75]

If bleeding cannot be controlled through endoscopy, options such as transcatheter arterial embolization (TAE) or surgical intervention should be considered. Although TAE has higher rebleeding rates compared with surgery, it is associated with significantly lower complication risks, shorter hospital stays, and no difference in mortality.[127,128] Hence, TAE is the preferred salvage therapy for patients with failed endoscopic therapy, while surgery is considered when TAE is unavailable locally or after failed TAE attempts.[75,124]

Novel endoscopic therapy—hemostatic powder spray

Hemostatic powder spray is a novel technique developed since 2013, offering a valuable solution for managing active peptic ulcer bleeding. Through air supply by the spraying system, the hemostatic powder can directly attach to bleeding surfaces under the endoscopy view.[129] Through the absorption of water molecules of the oozing blood, it becomes a physical barrier and concentrates clotting factors at the site of bleeding.[130] This non-touch technique can avoid heat coagulation thermal injury and sclerosis therapy-related mucosal damage.[131] Additionally, the hemostatic powder spray is easy to use, which can reduce the operational difficulty among endoscopy trainees.

TC-325 (Hemospray) and EndoClot are commonly used hemostatic powder spraying systems. Hemospray is the first and the most widely used hemostatic powder in the world. Hemospray is comprised of bentonite, a mineral powder that rapidly absorbs water in the blood, creating an adhesive physical barrier for mechanical tamponade.[132] After the bleeding stops, the powder falls off from the mucosa within 72 h without causing obstruction in the GI tract.[132] Hemospray was approved in 2018 for use in facilitating endoscopic hemostasis and reducing recurrent bleeding.[133] Hemospray monotherapy demonstrated high successful procedure rate (>95%) and high hemostatic rate (>90%) in bleeding peptic ulcers, even in Forrest IA lesions.[133–135] It can also serve as a rescue therapy when conventional standard endoscopic hemostasis fails, especially in malignant ulcer bleeding.[136,137] However, early fall-off of the Hemospray barrier increases the rebleeding risk within 72 h. Besides, Forrest IA peptic ulcers

are reported to be associated with a higher risk of rebleeding after Hemospray monotherapy.[138]

EndoClot consists of absorbable modified polymers sourced from plant starch. When in contact with blood, these polymers rapidly absorb water to create a protective gel matrix and concentrate coagulation factors at the bleeding ulcer.[139] Additionally, EndoClot has demonstrated the ability to stimulate fibroblasts and growth factors, thereby aiding in wound healing.[140] Similar to Hemospray, the adhesive material of EndoClot falls off within 24 h, causing a risk of early rebleeding after endoscopic treatment.[139] Hemospray and EndoClot share a similar successful hemostasis rate (>90%) and rebleeding rate (<20%) within 30 days.[141,142] Air blow injury is the major concern among the use of hemostatic powder spray. Numerous instances of visceral perforation have been observed after the administration of hemostatic powder.[143,144]

Several new hemostatic powder devices have emerged in the last decades, for example, UI-EWD (NexPowder, Nextbiomedical, Incheon, South Korea), and Ankaferd Blood Stopper (ABS, Ankaferd Health Products Ltd, Turkey). However, several concerns do not suggest this treatment modality to be used as a first-line therapy. The powders can block the endoscopic view and the bleeder, making subsequent rescue therapies difficult.[136] Furthermore, technical issues of catheter occlusion may occur before and during the spray, especially when the working channel is moist.[136] Therefore, hemostatic powder spray is commonly used as the last step during the endoscopic treatment. The 2019 consensus guidelines recommend the utilization of hemostatic powder sprays as a temporary solution to control bleeding when conventional endoscopic treatments are ineffective or inaccessible.[145] This strategy is especially advantageous in instances of malignant ulcers and difficult-to-contact bleeders (proximal lesser curvature of the stomach, posterior wall, and junction of the first and second portion of the duodenum).[145]

Future prospectives

Hemostatic gel emulsion may become another rescue solution for uncontrollable peptic ulcer bleeding. PuraStat, a novel transparent gel with self-assembling peptides, has been invented for treating hemorrhages from small vessels in the GI tract.[146] PuraStat gel includes three types of amino acids, which can be activated after contact with bodily fluid as a change in pH and salt concentration.[146] After activation, PuraStat transforms into matrix fibers to stick to and seal the blood vessel as a mechanical barrier.[146] PuraStat was first been applied to reduce delayed bleeding and improve wound healing after endoscopic resection in the GI tract, such as ESD.[147] For acute GI bleeding, the hemostatic gel also demonstrated a high hemostatic rate (90%) as a rescue therapy after conventional therapy.[148,149] The advantage of PuraStat over hemostatic powders is the transparency, which improved visualization and a chance for subsequent endoscopic interventions.[150] Further clinical trials using hemostatic gels are warranted to evaluate the efficacy of being the first-line therapy for peptic ulcer bleeding.

The combination of the powder spray system and hemostatic drugs is another possible solution for challenging bleeding ulcers. With the air supply from the spray system, medication powders with a local hemostatic effect can be directly brought to the bleeding site. TXA is an antifibrinolytic medication that inhibits fibrin degradation with a local effect, and the delivery of TXA powder has been proven to improve hemostasis and reduce the recurrent bleeding rate in peptic ulcers.[50] Based on our review, sucralfate can create a protective layer and promote mucosal healing with a local effect, which makes it a potential drug powder for a bleeding ulcer.[54] Through the precise drug powder spray, the drug dosage can be minimized to avoid possible adverse events. However, this idea about drug powder delivery in bleeding ulcers needs more studies for validation.

Conclusion

With the development of medications and endoscopic therapies, the successful rate of immediate hemostasis of peptic ulcers has been improved to over 90%, and the 30-day rebleeding rate has been reduced to nearly 10%. Gastroenterologists are still working on the perfect solution for challenging peptic ulcer bleeding. Hemostatic powder spray and hemostatic gel emulsion are potentially the final parts of the puzzle. How to avoid powder obstruction and maintain a clear endoscopic view are unsolved problems after hemostatic powder spray. Extending the powder/gel residence time on the ulcer can potentially reduce the rebleeding rate. Among novel pharmacologic treatments,

P-CABs have shown non-inferior efficacy to high-dose intravenous PPIs, which may also be beneficial before endoscopic treatment and after endoscopic treatment fails. A combination of conventional and novel treatment, including drugs and endoscopy, may become the mainstream approach for individual therapy. Clinical trials and real-world evidence are needed in the last mile toward the perfect solution for peptic ulcer bleeding.

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Not applicable.

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Meng-Hsuan Lu: Conceptualization; Writing – original draft.

Hsueh-Chien Chiang: Conceptualization; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Appendix

Abbreviations

APC	argon plasma coagulation
ESD	endoscopic submucosal dissection
Hp	*Helicobacter pylori*
MHFSC	monopolar hemostatic forceps with soft coagulation
NSAID	non-steroidal anti-inflammatory drug
OTSC	over-the-scope clip
P-CAB	potassium-competitive acid blocker
PGE1	prostaglandin E1
PPI	proton pump inhibitor
SRH	stigmata of recent hemorrhage
TAE	transcatheter arterial embolization
TTSC	through-the-scope clip
TXA	tranexamic acid