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Research Progress in Clinical Diagnosis and Treatment of Upper Gastrointestinal Bleeding

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Abstract

Upper gastrointestinal bleeding (UGIB) refers to the bleeding caused by the digestive tract above the flexor ligament, including esophageal, gastric, duodenal, pancreatic and biliary diseases, and lesions after gastrojejunostomy. UGIB is one of the common diseases in the clinical work of gastroenterology. There are many causes that can lead to upper gastrointestinal bleeding, which are mainly divided into two categories: one is non-variceal upper gastrointestinal bleeding (NVUGIB), and the other is variceal upper gastrointestinal bleeding (VUGIB). This article reviews various causes of UGIB and the latest progress in treatment, aiming to improve the efficiency of diagnosis and treatment in future clinical work, and reduce the risk of rebleeding and mortality.

Keywords

Upper Gastrointestinal Bleeding, Etiology, Diagnosis, Treatment

1. Introduction

Upper gastrointestinal bleeding (UGIB) refers to the bleeding originating from the esophagus, stomach or duodenum near the flexor ligament [1], which belongs to the emergency and critical cases commonly seen in gastroenterology. Patients may suffer from hemorrhagic shock or even threaten life safety due to excessive bleeding. Upper gastrointestinal bleeding is mainly divided into two types: one is non variceal upper gastrointestinal bleeding (NVUGIB), the other is variceal upper gastrointestinal bleeding (VUGIB). These two types of bleeding have different clinical manifestations, diagnosis and treatment. In order to further improve the cure rate of patients, improve the prognosis of patients, improve the diagnosis and treatment of the disease, and reduce the risk of rebleeding and mortality, this article will focus on the etiology, diagnosis and treatment of upper gastrointestinal

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bleeding, and make the following review.

2. Etiology of upper Gastrointestinal Bleeding

There are many causes of upper gastrointestinal bleeding. NVUGIB is one of the most common and important gastrointestinal diseases encountered in clinic. The main cause of NVUGIB is peptic ulcer bleeding [2], including acute gastric mucosal lesions, esophageal mucosal tearing (Mallory-Weiss syndrome, MWS) and tumors. In addition, stress ulcer and Dieulafoy disease can also cause gastrointestinal bleeding [3] [4]. In recent years, the cases of iatrogenic upper gastrointestinal bleeding, such as endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR), and polypectomy, are also increasing. The etiology of VUGIB is mainly esophageal and gastric variceal bleeding. In conclusion, the key to prevent upper gastrointestinal bleeding is to fundamentally eliminate the incentives and provide healthy life guidance to patients. Therefore, for patients with hematemesis, melena, bloody stool and other symptoms, we need to conduct a detailed examination to determine the etiology, so as to timely treat, improve the prognosis of patients, and avoid unnecessary complications and death risk.

2.1. Peptic Ulcer (PU)

PU is the most common NVUGIB, accounting for about 31% - 67% of UGIB [5]. Peptic ulcer is commonly seen in the clinic as gastric and duodenal ulcer. Generally, the disease has a good prognosis, but it is easy to recur, and can cause gastrointestinal bleeding, perforation and other complications, which are life-threatening when serious [6]. The pathogenic factors of peptic ulcer are complex. Helicobacter pylori (HP) infection, genetics, stress, drugs, irregular life, mental and psychological factors can lead to its onset, among which helicobacter pylori (HP) infection is considered to be an important influencing factor of peptic ulcer [7]. The persistent immune inflammatory injury induced by HP infection is one of the important mechanisms of peptic ulcer formation, and it also affects the disease process of patients.

2.2. Acute Gastric Mucosal Lesion (AGML)

There are three basic pathological features of AGML: gastric mucosal erosion, superficial ulcer, and hemorrhage. It is a major cause of UGIB, accounting for about one-third of the total incidence. AGML is a common disease. Patients with severe AGML will have symptoms of upper gastrointestinal bleeding, which is easy to cause death.

2.3. Mallory-Weiss Syndrome (MWS)

In recent years, with the popularity of emergency gastroscopy, the proportion of MWS in the etiology of UGIB has an upward trend. The statistics of Gralnek *et al.* [8] showed that it accounted for 4% - 7% of the etiology of UGIB. The pathological feature of NWS is the longitudinal shallow mucosal tear at the gastroesophageal

junction, which includes the mucosal tear in the lower and middle segments of the esophagus, and can also occur in the proximal part of the stomach. Most patients with MWS are self limiting and the disease will not recur [9]. But in the group of patients with portal hypertension or coagulation dysfunction, the risk of rebleeding is significantly increased [10].

2.4. Tumor Hemorrhage

Malignant tumors, such as gastric cancer, liver cancer and biliary tract tumors, may undergo necrosis and rupture with the increase of tumor volume, resulting in hemorrhage. A foreign study showed that the bleeding rate of patients with gastrointestinal tumors is between 9.5% - 20% [11] [12]. Because hemostatic measures for tumor bleeding can not cure the primary tumor, the rebleeding of patients is relatively common [13] [14]. Therefore, once tumor patients are complicated with gastrointestinal bleeding, the risk of rebleeding is high, which often indicates a poor prognosis.

2.5. Stress Ulcer (SU)

SU is an acute injury of gastric and duodenal mucosa caused by severe stress reaction, which is manifested by mucosal erosion and superficial ulcer [15]. Coagulation dysfunction, mechanical ventilation and renal replacement therapy are important risk factors for SU [16]. After stress reaction, the protective barrier of gastrointestinal tract will be damaged, which may cause erosion and ulceration of gastrointestinal mucosa, and even cause bleeding. According to a foreign study [17], the mechanism behind SU is not completely clear, but there is a hypothesis that SU is caused by reduced mucosal blood flow, ischemia and reperfusion injury [18], although most erosion is superficial and asymptomatic, in some cases, they may lead to clinically important bleeding or perforation [17].

2.6. Dieulafoy Disease

Dieulafoy disease is a relatively rare but potentially life-threatening disease. It is most commonly found in the tortuosity of the small arteries of the stomach, which may cause blood loss and serious gastrointestinal bleeding. Patients with Dieulafoy disease usually have no obvious symptoms clinically until patients have symptoms of gastrointestinal bleeding such as hematemesis, hematochezia or melena [19]. Dieulafoy disease accounts for 6.5% of NVUGIB etiologies, Dieulafoy disease lesions are composed of malformed blood vessels. The diameter of this malformed artery is usually 1 - 3 mm, protruding from the submucosa into the mucosa. There is fibrin like necrosis at the bottom of the lesion, and 70% of these lesions are located in the stomach [20]. Dieulafoy lesion bleeding is most often associated with cardiovascular disease, chronic kidney disease, hypertension, peptic ulcer disease, diabetes and long-term use of non steroidal anti-inflammatory drugs (NSAIDs) and anticoagulant drugs and other comorbidities [21]. Dieulafoy disease in adults, the incidence of men is twice that of women [22].

2.7. Esophagogastric Variceal Bleeding (EGVB)

A study showed that [23] the probability of developing esophageal and gastric varices is related to the severity of liver tissue damage. Once varices rupture and bleed, the mortality rate within 6 weeks after bleeding is as high as 20%. When the portal pressure gradually increases, the vascular resistance gradually increases, the systemic circulation backflow obstruction and blood stasis occur, resulting in the increase of circulating blood volume, the formation of collateral circulation between the systemic circulation and portal vein, the vascular tension of varicose veins gradually increases, the volume becomes larger, the diameter is thicker, and the degree of varicose veins is aggravated, thus making the vascular wall more fragile [24], and variceal bleeding is more likely to occur. Although with the development of technology, the mortality rate of EGVB has been significantly reduced, but the mortality rate is still 7% - 12% [23].

3. Diagnosis and Differential Diagnosis of Upper Gastrointestinal Bleeding

The clinical symptoms of upper gastrointestinal bleeding (UGIB) include hematemesis, melena and hematochezia [25], and also atypical symptoms such as dizziness, fatigue and syncope. The main diagnostic criteria of UGIB include: significant medical history: chronic and regular right upper abdominal pain, history of liver cirrhosis, combined with stones, tumors, excessive alcohol consumption, etc.; clinical features of UGIB: black or tarry stools, with or without hematemesis, positive fecal occult blood test, coffee-colored or brownish blood in hematemesis, if the patient has a rapid and large amount of bleeding, the blood in hematemesis may be accompanied by blood clots; symptoms of hypovolemic shock: when a patient has massive bleeding and leads to hypovolemic shock, the clinical manifestations are dizziness, palpitations, fatigue, sweating, cold and clammy skin, rapid and weak pulse, and decreased blood pressure. In severe cases, shock may occur; fever: most patients with UGIB will have a low fever within 24 hours, with a body temperature generally not exceeding 38˚C. The fever symptoms last for 3 to 7 days. If the body temperature exceeds 39˚C and the symptoms persist for more than 7 days, it may indicate that the patient has complications. Therefore, when clinicians receive patients, they should pay attention to asking about the patient's history of peptic ulcer, liver disease, use of anticoagulant or antiplatelet drugs and analgesics, and inquire about the patient's drinking, smoking and dietary habits. They should also pay attention to observing whether the patient has an anemic appearance, liver disease appearance, liver palms, spider nevi, etc., which are also helpful for the diagnosis of UGIB. In addition, laboratory tests can also help us determine the treatment plan. Fecal occult blood test can help us detect upper gastrointestinal bleeding in patients. The fecal occult blood test of patients with peptic ulcer is positive in the short term and turns negative after successful treatment; the fecal occult blood test of patients with digestive tract tumors is continuously positive. In the early stage of bleeding in UGIB patients, blood

tests will show significant changes. Anemia occurs 3 to 4 hours after bleeding, and reticulocytes show an upward trend within 24 hours of bleeding. If it continues to rise, it indicates that the patient is continuously bleeding; white blood cell count increases 2 hours after bleeding and returns to normal 2 to 3 days after successful hemostasis. Blood urea nitrogen levels show an upward trend several hours after bleeding, reaching the highest value within 24 to 48 hours, and returning to normal 3 to 4 days after successful hemostasis. If it continues to rise, it indicates that the patient is continuously bleeding; if the urea nitrogen level remains elevated after successful hemostasis and blood volume is replenished, it may indicate that the patient has combined renal failure.

The differential diagnosis of upper gastrointestinal bleeding (UGIB) involves various diseases and conditions, and it needs to be differentiated from hemoptysis, bleeding from the oral, nasal and pharyngeal regions, and lower gastrointestinal bleeding. Hemoptysis is mostly caused by respiratory tract bleeding due to respiratory system diseases. Before the bleeding, there are often symptoms such as coughing, expectoration, and itchy throat. The blood is usually coughed up and is mostly bright red, often accompanied by bubbles. In contrast, UGIB is often accompanied by symptoms such as nausea, vomiting, abdominal pain, and hematemesis. Bleeding from the oral, nasal and pharyngeal regions is often caused by local injuries or inflammation. The blood can be spat out through the mouth, and the bleeding site is usually easy to identify. Attention should be paid to whether there are ulcers in the oral cavity, pharynx and nose. After bleeding, there are usually no typical manifestations of upper gastrointestinal bleeding such as hematemesis and melena. Lower gastrointestinal bleeding is mainly manifested as hematochezia, which is mostly bright red or dark red, and there is usually no hematemesis. The bleeding site can be identified through colonoscopy and other examinations. There are significant differences in symptoms, bleeding characteristics and examination results between upper and lower gastrointestinal bleeding. In addition, it should be noted that some drugs and foods may cause changes in stool color, similar to melena, and a detailed history should be taken to make a differential diagnosis.

However, the history, clinical manifestations and laboratory tests can not directly determine the bleeding site and etiology. Some patients' symptoms are atypical, such as dizziness, fatigue, syncope, etc., which are easy to be ignored or misdiagnosed. It is difficult to make a diagnosis based on symptoms alone, which needs to be comprehensively judged in combination with endoscopy. Endoscopy is the most direct and accurate method for the diagnosis of UGIB. It can directly observe the lesions of esophageal, gastric and duodenal mucosa, such as inflammation, ulcer, tumor, etc., and can take tissue for pathological examination to clarify the nature of the lesions. At the same time, it can also stop bleeding under endoscopy. Therefore, in the diagnosis of UGIB, a variety of methods such as history, clinical manifestations, laboratory examination and endoscopy should be comprehensively considered to improve the accuracy and timeliness of diagnosis.

4. Treatment of Upper Gastrointestinal Bleeding

When treating patients with UGIB, we should follow the principle of specific analysis of specific problems, provide timely and targeted treatment for patients with different degrees of severity, improve the cure rate of patients, prevent a series of complications, and ensure the prognosis of patients to the greatest extent. International guidelines have updated the content of the best treatment plan for UGIB [8] [26] [27], which can be generally divided into three stages: pre-endoscopic, endoscopic, and post-endoscopic treatment.

4.1. Pre Endoscopic Treatment

Pre endoscopic treatment includes drug therapy, blood transfusion, and timing of endoscopic examination. Proton pump inhibitors (PPIs), vasoactive drugs, and prophylactic antibiotics should be given to UGIB patients in different clinical situations [28]. Due to the relatively low rebleeding rate and mortality, restrictive blood transfusion should be advocated in clinical treatment. For patients without cardiovascular diseases, the recommended hemoglobin threshold for blood transfusion is lower than 80 g/L. For patients with cardiovascular diseases, the threshold should be higher. When considering VUGIB, excessive blood transfusion should be avoided as it may exacerbate the bleeding. Blood transfusion is recommended when the hemoglobin level is less than 70 g/L. Although some patients with UGIB have no significant abnormalities in platelet count, if they have a history of taking antiplatelet drugs, even if they have stopped taking the drugs, the antiplatelet effect lasts for 8 - 10 days. Therefore, platelet transfusion is often given to patients during antiplatelet treatment. Additionally, it is worth noting that while treating hemorrhagic shock, we should pay more attention to the type of bleeding, the bleeding site, and the patient's cardiac function to further improve the cure rate. The rehydration treatment of UGIB is an important treatment measure in emergency. The main purpose is to rapidly replenish blood volume, maintain blood pressure stability, prevent shock, and provide conditions for further treatment. The commonly used acid suppressive drugs in clinic include PPIs and H2 receptor blocker. PPIs is currently the preferred acid suppressive drug in clinic. Although some studies have shown that [29] the use of PPIs before endoscopic treatment has no obvious effect on reducing the rebleeding rate, operation rate or mortality of patients, the use of PPIs before endoscopic examination can reduce the high-risk bleeding signs observed under endoscopy and reduce the implementation of endoscopic hemostasis measures. In addition, it is also recommended to use PPIs before endoscopy when patients with a previous history of liver disease or cirrhosis cannot rule out ulcer bleeding. Vasoconstrictors commonly used in clinic include somatostatin and its analogues and vasopressin and its analogues. Somatostatin is a ring-shaped active peptide composed of multiple amino acids. It can effectively promote the vasoconstriction of internal organs, reduce the release of vasoactive substances, optimize the hyperdynamic circulation of internal organs, reduce the blood flow of portal vein and its collateral

vessels, further reduce the pressure of portal vein, and achieve hemostatic effect. Patients with cirrhosis complicated with UGIB also have a certain chance of rebleeding after successful hemostasis and discharge, which will adversely affect the prognosis of patients. Prophylactic use of antibiotics can improve the rebleeding situation of patients and reduce the rebleeding rate. Therefore, in the actual clinical practice, for patients who want to use antibiotics prophylactically, due to the consideration of the specific situation of patients, such as bacterial resistance, etc., and at the same time, closely monitor the changes of the disease, select the appropriate antibiotics for treatment. Antithrombotic drugs include antiplatelet drugs and anticoagulant drugs. These drugs produce antithrombotic effects by inhibiting the function of coagulation factors or the release, aggregation, and adhesion of platelets. Currently, there is still controversy in clinical whether patients with gastrointestinal bleeding after taking antithrombotic drugs continue to take antithrombotic drugs after hemostasis treatment. How to improve the prognosis of patients to the greatest extent still needs further research.

The management of antiplatelet drugs in patients with UGIB is complex, and the specific situation of patients needs to be comprehensively considered. The author believes that if antiplatelet drugs are not necessary, such as the use of aspirin as the primary prevention of cardiovascular events, they should be discontinued and evaluated when necessary. For patients with secondary prevention treated with aspirin alone or dual antiplatelet therapy, mild bleeding does not need to be discontinued. When the patient has obvious bleeding, stop aspirin first. If there is life-threatening active bleeding, stop all antiplatelet drugs. For severe bleeding caused by taking antiplatelet drugs, platelet function monitoring can be carried out. After the abnormal platelet function is confirmed, platelet transfusion can be carried out to improve the bleeding.

4.2. Endoscopic Treatment

Endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS) and endoscopic histoacryl injection (EHI) are commonly used in the clinical treatment of VUGIB patients.

EVL is an important treatment for esophageal varices. It plays a key role in primary prevention, secondary prevention and emergency hemostasis treatment. Complications of EVL include perforation, infection, bleeding, ulcer, esophageal stenosis, dysphagia, post sternal pain, etc., but it also has the advantages of fast onset, small trauma, high safety, and has been widely used in clinic. The combination of EVL vasoactive drugs has become the preferred treatment for the treatment of esophageal and gastric variceal bleeding in cirrhosis [30]. However, EVL needs to be reviewed regularly and ligated again if necessary. For some severe variceal bleeding, hemostasis may need to be combined with other treatment methods.

EIS refers to injecting sclerosant into the lumen or near the blood vessels of varicose veins under endoscopy, destroying vascular endothelial cells, followed by leukocyte infiltration and thrombosis, causing coagulative necrosis of vascular

lumen and surrounding mucosal tissue to form fibers to block blood vessels, so as to achieve the purpose of hemostasis. EIS has limitations, such as rapid dilution of sclerosing agents and increased distal embolization risk due to rapid blood flow and abundant vasculature, and EVL is superior to EIS in rebleeding rate, complication rate, and varicose eradication rate [31]. Commonly used hardeners include ethoxysclerotol, sodium morrhuate, sodium tetradecyl sulfonate, oleic aminoethanol, absolute ethanol, etc., but sodium morrhuate has been rarely used in clinic due to many side effects. During EIS operation, the injection position and dose of hardener need to be precisely controlled. If the injection location is inaccurate or the dose is too large, it may lead to serious complications. When operating under endoscopy, the visual field may be limited, especially in the upper esophagus and other parts. This may lead to inaccurate injection location and increase the risk of complications. Therefore, endoscopists need to have rich experience and skilled operation skills.

Tissue glue will polymerize and solidify rapidly after contacting with blood. This property makes it have a significant hemostatic effect on variceal bleeding, and can prevent patients from bleeding again and eliminate varicose veins. For patients with vugib, EHI can improve the hemostasis rate and variceal elimination rate, reduce the risk of rebleeding and variceal recurrence rate, and reduce the incidence of complications. It has the advantages of good curative effect and high safety. However, the polymer formed by tissue glue will cause persistent irritation to the gastric wall, resulting in pain behind the sternum of patients, and may also lead to rebleeding of incompletely closed varicose veins, and local tissues may form ulcers after tissue glue injection. These ulcers may cause pain and discomfort, and under the stimulation of gastric acid, the ulcer wound will further aggravate, increasing the risk of rebleeding.

Endoscopic treatment methods commonly used in NVUGIB patients include endoscopic drug injection and mechanical hemostasis. Endoscopic drug injection hemostasis mainly through the injection of hemostatic drugs to the bleeding lesions and vascular stumps, so that the submucosal tissue around the bleeding lesions swells, thus compressing the bleeding site, and then combined with the hemostatic function of drugs to stop bleeding. Its mechanism of action is that epinephrine has a strong vasoconstrictor function, and can inhibit the aggregation of platelets, resulting in the swelling of the surrounding tissue of the bleeding focus to achieve the purpose of hemostasis. However, after the hemostatic effect of drugs disappears, it is easy to cause recurrent bleeding of the bleeding focus, and the treatment effect is limited, which is not conducive to the prognosis of patients. The American Gastroenterological Association stated that epinephrine treatment should not be used alone, but in combination with other treatment regimens [32]. Endoscopic mechanical hemostasis is mainly divided into titanium clip and over-the-scope clips (OTSC) hemostasis. The hemostatic effect of endoscopic titanium clip is relatively long-lasting, which can significantly reduce the risk of rebleeding, improve the coagulation function of patients, reduce the stress reaction of

patients, and reduce the incidence of complications, with good therapeutic effect and safety. The difference between OTSC and other types of hemostatic clamps is that OTSC can be released in a closer position under the endoscopic field of vision, and it can accurately operate the bleeding focus with the assistance of transparent membrane. Moreover, OTSC has greater clamping force and stronger bite force, and it can still be easily clamped in places with heavy inflammatory reaction and difficult operation such as scar tissue. Studies have shown that OTSC may be better than conventional hemostatic clip treatment for NVUGIB patients with high risk of rebleeding [33], but some scholars believe that OTSC should not be routinely used as the first-line endoscopic hemostasis method for PU bleeding. For patients with ulcers located at the top of large vessels and large-area ulcers or ulcers located at high-risk sites, OTSC can be selected as the initial treatment, because these patients will benefit from this treatment method without overtreatment [34].

4.3. Post Endoscopic Treatment

As an adjunct to endoscopic treatment, high-dose oral PPIs can be used to prevent rebleeding after endoscopic hemostasis treatment. High dose oral PPI is defined as at least 80 mg esomeprazole (or the equivalent dose of other PPIs), and the high-dose oral PPIs should be maintained for at least 3 days, because this is the period with the highest risk of recurrent bleeding. If the patient's condition remains stable, then the standard dose of oral PPI can be resumed [26].

5. Artificial Intelligence (AI): A New Direction in the Diagnosis and Treatment of UGIB

AI can predict the efficacy and safety of different drug treatment plans based on the patient's disease characteristics, past medical history, and drug reactions, providing doctors with references to select the most suitable drug treatment plan, improving the success rate of drug treatment and reducing adverse reactions. In endoscopic examinations, AI can analyze endoscopic images through deep learning algorithms to automatically identify bleeding sites and lesion features. For instance, some studies have used convolutional neural networks to analyze capsule endoscopy images and detect signs of bleeding, assisting doctors in more accurately locating the bleeding source and reducing the possibility of missed diagnoses and misdiagnoses. For patients where the source of bleeding cannot be clearly identified through endoscopic examinations or where bleeding cannot be controlled, angiography is an important diagnostic method [35]. AI models can analyze digital subtraction angiography images to identify images of active bleeding, helping doctors more accurately assess the bleeding situation and providing a basis for subsequent interventional treatment. Based on the patient's treatment effect, risk factors, etc., AI can develop personalized follow-up plans, reminding doctors to conduct more frequent follow-ups and monitoring for high-risk patients, promptly detecting signs of recurrence and taking measures to reduce the

risk of rebleeding. Patient education tools developed using AI technology can provide personalized health education information to patients, helping them better understand their condition and master self-management methods, such as dietary adjustments and drug administration precautions, improving patients' treatment compliance and self-management abilities, and promoting recovery.

6. Summary

The key of UGIB treatment is timely and effective hemostasis. In recent years, with the continuous development of endoscopic technology, endoscopic treatment has become one of the main treatment methods of UGIB, which can significantly improve the success rate of hemostasis, reduce the rebleeding rate and mortality, and its safety has also been widely recognized. In conclusion, the prevention and treatment of UGIB require the joint efforts of our medical staff. We believe that with the continuous development of science and technology, the prevention and treatment of UGIB will make greater breakthroughs and progress, and make greater contributions to the protection of patients' health and life safety.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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