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Guideline

Guidelines for the Management of Esophagogastric Variceal Bleeding in Cirrhotic Portal Hypertension

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Abstract

To standardize the diagnosis, treatment, and management of esophagogastric variceal bleeding (EVB) in patients with cirrhotic portal hypertension, the Chinese Society of Hepatology, the Chinese Society of Gastroenterology, and the Chinese Society of Digestive Endoscopy of the Chinese Medical Association brought together relevant experts, reviewed the latest national and international progress in clinical research on EVB in cirrhotic portal hypertension, and followed evidence-based medicine to update the Guidelines on the Management of EVB in Cirrhotic Portal Hypertension. The guidelines provide recommendations for the diagnosis, treatment, and management of EVB in cirrhotic portal hypertension and with the aim to improve the level of clinical treatment of EVB in patients with cirrhotic portal hypertension.

Keywords: Guideline; Management; Esophagogastric variceal bleeding; Cirrhosis; Portal hypertension.

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ACLF, acute-on-chronic liver failure; AEVB, acute esophageal-gastric variceal bleeding; AFP, alpha-fetoprotein; ARB, angiotensin receptor blocker; BRTO, balloon-occluded retrograde transvenous obliteration; CSPH, clinically significant portal hypertension; CT, computed tomography; EASL, European Association for the Study of the Liver; EIS, endoscopic injection sclerotherapy; eTIPS, early transjugular intrahepatic portosystemic shunt; EUS, endoscopic ultrasound; EVB, esophagogastric variceal bleeding; EVL, endoscopic variceal ligation; GOV, gastroesophageal varices; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ICU, intensive care unit; IGV, isolated gastric varices; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; NSBBs, nonselective beta-blockers; PIVKA, protein induced by vitamin K deficiency or vitamin K antagonist-II protein; PPAR, peroxisome proliferator-activated receptor; PPIs, proton pump inhibitors; pTIPS, preemptive transjugular intrahepatic portosystemic shunt; PVT, portal vein thrombosis; RC, red color; RFs, risk factors; SBP, spontaneous bacterial peritonitis; SEMS, self-expandable esophageal metallic stent; TCM, traditional Chinese medicine; TE, transient elastography; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinases; TIPS, transjugular intrahepatic portosystemic shunt.

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Overview

Portal hypertension refers to a group of clinical syndromes caused by elevated pressure in the portal venous system due to different causes, the most common of which is liver cirrhosis. The basic pathophysiological features of portal hypertension include obstruction of blood flow and/or increased blood flow in the portal venous system, increased static pressure in the portal vein and its tributaries, and the formation of collateral circulation. The main clinical manifestations include ascites, gastroesophageal varices (GOV), esophagogastric variceal bleeding (EVB), and hepatic encephalopathy (HE), among which EVB has the highest mortality rate and is one of the most common emergency conditions associated with the digestive system.

To standardize the prevention, diagnosis, and treatment of EVB in cirrhotic portal hypertension, the Chinese Society of Hepatology, Chinese Society of Gastroenterology, and Chinese Society of Digestive Endoscopy developed a consensus on prevention and treatment for GOV and variceal hemorrhage in liver cirrhosis in 2008, followed by the guidelines for the diagnosis and treatment of esophageal and gastric variceal bleeding in cirrhotic portal hypertension in 2016.[1,2] The progress of basic and clinical research has allowed a deeper understanding of the diagnosis and treatment of upper gastrointestinal bleeding in cirrhosis. In recent years, academic associations, such as the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of Liver Diseases, have successively developed and updated a series of relevant guidelines and consensus statements, including the Baveno VII consensus,[3–7] which provides recommendations for the prevention and treatment of upper gastrointestinal bleeding in patients with cirrhosis.

The Chinese Society of Hepatology, Chinese Society of Gastroenterology, and Chinese Society of Digestive Endos-

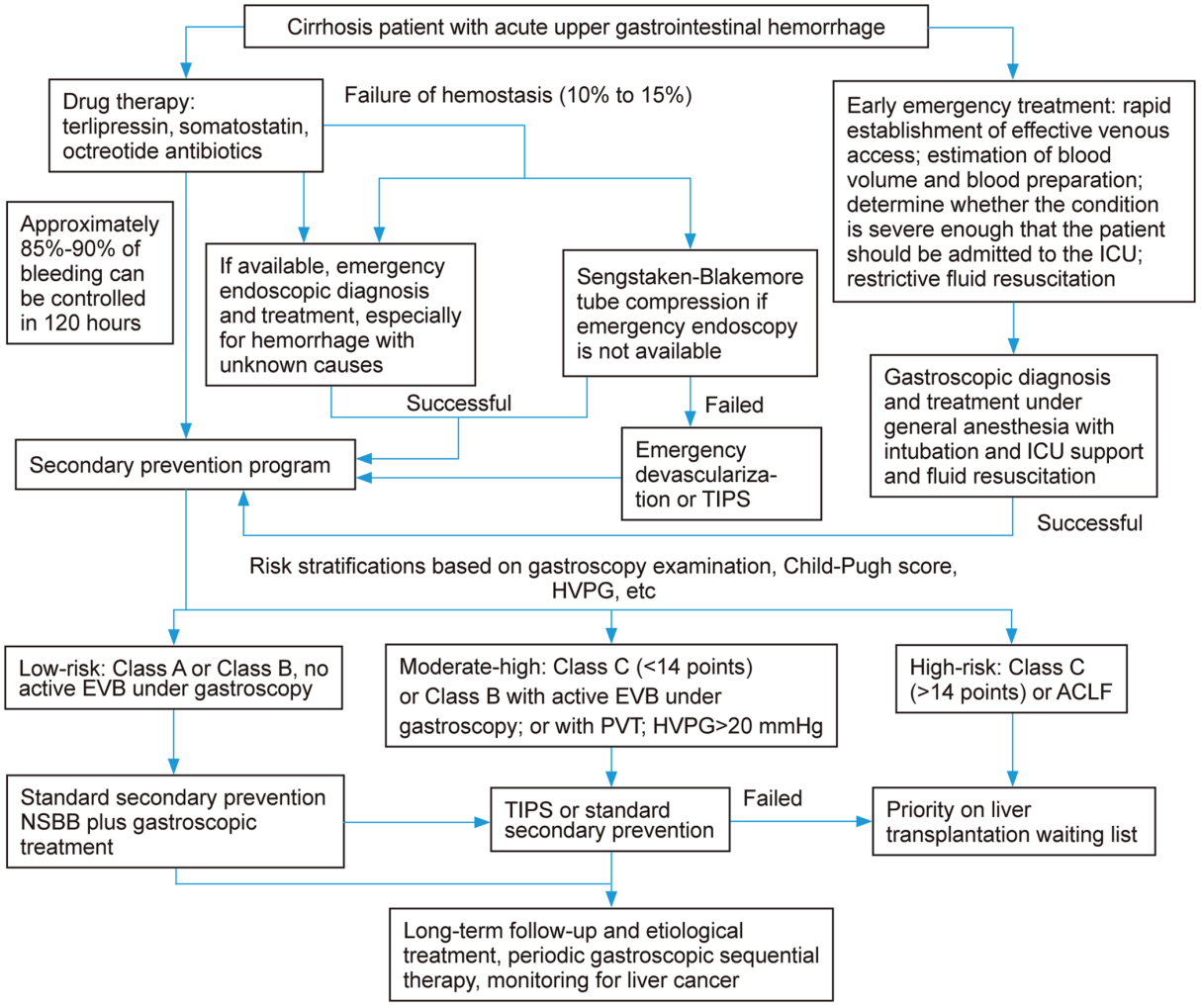

Fig. 1. Recommended flow of clinical management of acute upper gastrointestinal bleeding in liver cirrhosis. ACLF, acute-on-chronic liver failure; EVB, esophageal variceal bleeding; HVPG, hepatic venous pressure gradient; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

copy have organized relevant experts to revise the guidelines, with the aim of providing guidance on the diagnosis and treatment of cirrhosis. The guidelines aim to be based on evidence-based medicine; therefore, a steering committee comprised of a secretary group and expert panel (including corresponding experts) was established, which was comprised of experts specializing in liver diseases, gastrointestinal diseases, endoscopy, infectious diseases, surgery, intervention, tumor, traditional Chinese medicine (TCM), pharmacology, nursing, and clinical research methodology.

The main purpose of these guidelines is to help clinicians specializing in liver diseases, gastrointestinal diseases, or infectious diseases in tier two and above hospitals make appropriate decisions on the diagnosis and treatment of EVB. However, the guideline is not mandatory standards and cannot include or resolve all problems in the diagnosis and treatment of upper gastrointestinal bleeding in cirrhosis. Therefore, while caring for every patient, clinicians should follow the principles of this guideline, fully understand the disease condition, seriously consider the views and wishes of the patient, and develop a comprehensive and individualized diagnosis and treatment plan based on local medical resources and practical experience (Fig. 1). The level of evidence and strength of recommendations in the guidelines were graded according to the (Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Table 1).

Natural history, pathogenesis, and classification of GOV

Cirrhosis

Stage of liver cirrhosis: In China, the natural history of liver cirrhosis can be divided into compensated, decompensated, recompensated, and/or reversed liver cirrhosis, according to clinical manifestations.[8]

The onset of liver cirrhosis is usually insidious, and many early-stage patients are asymptomatic. International guidelines divide liver cirrhosis into six stages: compensated (stages 1 and 2), decompensated (stages 3, 4 and 5), and late decompensated (stage 6) cirrhosis, according to the presence of complications such as ascites, EVB, and HE. The annual mortality rate of patients with stages 5 and 6 was 88%. The clinical characteristics of each stage are summarized in Table 2.

Noninvasive examination techniques of portal hy-

Table 1. Level of evidence and strength of recommendations

Quality of evidence	
High (A)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low or extremely low (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Recommended strength level	
Strong (1)	There is a strong belief that that the intervention will do more good than harm or do more harm than good.
Weak (2)	The balance of benefits and harms is uncertain, or the quality of the evidence shows comparable benefit and harms.

pertension in liver cirrhosis: The liver stiffness is correlated with the hepatic venous pressure gradient (HVPG) and can be used for the auxiliary diagnosis of portal hypertension in liver cirrhosis.[9] Clinically significant portal hypertension (CSPH) is defined as an HVPG ≥ 10 mmHg. CSPH can be estimated by noninvasive examination techniques. For patients with cirrhosis of most etiologies, CSPH should be considered if liver stiffness measurement (LSM) is >25 kPa, or LSM is between 20 and 25 kPa combined with a platelet count below the lower limit of normal; thus, LSM<15 kPa plus a platelet count above the lower limit of normal can be used to rule out CSPH in most cases.[10] Transient elastography is the most convenient noninvasive technique for diagnosing liver fibrosis and early cirrhosis. Liver fibrosis and cirrhosis of different etiologies have different LSM cutoff values (Table 3).[11]

Contrast-enhanced multislice computed tomography (CT) is a widely used noninvasive examination method. It does not require sedatives and is well tolerated by patients, allows simultaneous detection of liver cancer and other lesions, and allows three-dimensional (3D) post-processing of imaging data, after which the displayed portal vein and its branches can be used to guide decision-making and surgical interventions with transjugular intrahepatic portosystemic shunt (TIPS). Therefore, it is more cost-effective.[12]

Contrast-enhanced multislice CT can distinguish submucosal GOV from periesophageal GOV and is closely related to the endoscopic classification. In patients with active EVB, the CT contrast can reach the esophagus, while in patients with inactive EVB, the contrast enhancement is often seen in the portal vein and parallel vascular pathways.[13]

Gastroscopy: Gastroscopy is the gold standard for diagnosing GOV and EVB. As an invasive examination, it remains the primary method for detecting GOV and assessing the risk of EVB.[14] Endoscopic ultrasound (EUS) can provide more information on changes in blood flow in the esophagus and gastric mucosa, especially in the differential diagnosis of early gastric varices and other lesions in the gastric fundus.[15]

Pathogenesis and assessment of risk factors

Liver cirrhosis of any etiology can induce portal hypertension; portal pressure is the product of intrahepatic vascular resistance along with portal blood flow. In liver cirrhosis, there is a large amount of neovascularization and sinusoidal hepatic capillarization in the area of hepatic fibrosis, resulting in increased intrahepatic blood flow and resistance. Portal hypertension also promotes angiogenesis of hepatic vein branches and formation of portal-systemic collateral circulation, after which the dilation of splanchnic vessels leads to increased blood flow without reduction of intrahepatic resistance. Therefore, spontaneous portosystemic shunts are not effective for decompression and portal hypertension persists.[16]

GOV should be determined in patients with compensated cirrhosis. The risk of developing liver decompensation and mortality in patients with GOV is significantly higher than in those without GOV. Overall, GOV can be detected in approximately 50% of patients with cirrhosis and is closely related to the severity of liver disease. GOV occurs in approximately 40% of patients with Child-Pugh class A and 85% of patients with Child-Pugh class C. The incidence of gastric varices is

Table 2. Clinical features of the stages of liver cirrhosis

Stage	**Compensated cirrhosis**			**Decompensated cirrhosis**			**Late decompensated cirrhosis**
	Stage 1a	**Stage 1b**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	**Stage 6**
Characteristics	No clinically significant portal hypertension, no gastrointestinal varices	Clinically significant portal hypertension without gastrointestinal varices	Esophagogastric varices without bleeding or ascites	Ascites without bleeding of the esophagogastric varices, with or without esophagogastric varices	Esophagogastric varices bleeding, with or without ascites or HE	More than two decompensation events	Refractory ascites, persistent encephalopathy or jaundice, infection, renal and other organ dysfunctions
Key points for attention	Prevent clinically significant portal hypertension	Prevent varicose veins		Prevent further deterioration of liver function in decompensated cirrhosis and reduce mortality		Reduce mortality	
	Prevent hepatic decompensation						

Table 3. The diagnostic cutoff values of LSM for liver cirrhosis in different states and of different etiologies

Common etiologies	Stratification by liver function	Cutoff value to diagnose cirrhosis in kPa	Cutoff value to rule out the diagnosis of cirrhosis in kPa
Chronic hepatitis B	ULN<ALT<5×ULN, normal bilirubin	17.0	10.6
	Normal ALT and bilirubin	12.0	9.0
Chronic hepatitis C	NA	14.6	10.0
Nonalcoholic fatty liver disease	NA	15.0	10.0
Alcoholic liver disease	NA	20	12.5

ALT, alanine aminotransferase; LSM, liver stiffness measurement; NA, not applicable; ULN, upper limit of normal.

approximately 20%, and the incidence of bleeding within 2 years is approximately 25%.[17] The annual incidence of EVB is 5~15%, and the 6-week mortality rate can be as high as 20%.

Risk factors (Rfs) for GOV bleeding include the severity of GOV, the red color (RC) sign, and the Child-Pugh classification. There is a linear positive correlation between the severity of GOV and diameter of the varicose vein, and the course of liver disease is the main determinant of varicose vein progression.[18] Mild varicosity, defined as varicose veins <5 mm in diameter, does not need temporary preventive treatment;[19] however, contrast-enhanced multislice CT should be performed to reconstruct the portal vein branches in 3D to better understand the overall changes in the portal vein branches caused by portal hypertension. After the diagnosis of liver cirrhosis, upper abdominal contrast-enhanced multislice spiral CT and gastroscopy findings should be reviewed regularly. The frequency depends on the severity of liver cirrhosis and GOV.

HVPG is an effective method for assessing the risk of portal hypertension. Portal hypertension is defined as an HVPG of >5 mmHg (normal range, 3~5 mmHg). HVPG>10 mmHg is a predictor of varicose vein formation and decompensation of liver cirrhosis, with HVPG>20 mmHg indicating a poor prognosis.[19] It is agreed that patients are at a minimal risk of EVB if the HVPG is <12 mmHg. Patients with HVPG ≤12 mmHg or those at a 10% reduction from baseline (defined as HVPG responders) are also at a lower risk of EVB recurrence, ascites, HE, and death. However, the detection of HVPG is an invasive procedure. When CSPH is diagnosed using noninvasive detection methods, or liver cirrhosis is confirmed by contrast-enhanced multislice CT and gastroscopy, it is not recommended to perform invasive examinations only for the assessment of HVPG.

Other important predictors include the diameter of the varicose vein and the liver reserve. The wall tension of the varicose vein, pressure force, and location of the varicose vein are the primary factors contributing to vessel rupture. The diameter of the vessel is closely correlated with the tension of the vascular wall and the HVPG. Under the same intravascular pressure, the larger the diameter, the greater the tension of the vessel wall, and the more likely it is to rupture. The rate of late bleeding recurrence in patients without EVB prophylaxis is approximately 60%, most of which occurs within 1–2 years of the first bleeding. Child-Pugh class, albumin level, and international normalized ratio (INR) are associated with CSPH and can be used for risk assessment in patients with compensated and decompensated cirrhosis.[20] Three criteria, including Child-Pugh class C, INR>1.5, portal vein diameter >13 mm, and significant thrombocytopenia, can predict the possibility of varicose veins in patients with liver cirrhosis; for those who met none, one, two, or three of the criteria, the incidence rates of esophageal varices were <10%, 20–50%, 40–60%, and >90%, respectively. Cirrhotic patients who meet one or more of the three criteria will be considered eligible for endoscopic screening for varicose veins and primary prevention of EVB. Model for end-stage liver disease (MELD) scores can be adopted to predict the development of hepatic decompensation in patients without varicose veins and can also be used to predict 6-week mortality after variceal bleeding.[21]

Grading of GOV

There are differences in the endoscopic classification and grading standards of GOV between China and other countries. While the Sarin classification is the most commonly used in other countries, this guideline recommends the LDRf classification[22] as the GOV classification and recording method of China. The LDRf classification is described and recorded according to three factors: (1) location of the varicose vein (location, L), (2) diameter of the varicose vein (diameter, D), and (3) Rf. The classification method is convenient for memorization and recording, and can cover varicose veins formed throughout the digestive tract. It integrates functions of recording, classification, treatment choice, and timing. In addition, the LDRf classification provides recommendations for treatment choice and timing according to the sites, diameters, and vascular phenotypes of varicose veins[2,23] The format of LDRf classification is as follows: LXx D0.3-5.0 Rf 0,1,2. LXx: The uppercase X represents the first letter of the English name of the organ; for instance, esophagus: e, gastric: g, duodenum: d, jejunum: j, ileum: i, and rectum: r. The lowercase x represents the segment of the organ where the varicose veins are located. Taking the esophagus as an example, the superior segment: s, middle segment: m, and inferior segment: i are designated as Les, Lem, and Lei, respectively. The isolated gastric varices are recorded as Lg, wherein Lgf, Lgb, and Lga represent the gastric varices in the fundus, body, and antrum, respectively. Esophageal varices that extend to the gastric fundus are recorded as Leg. If the varices involve multiple segments, combined codes of the different sites are used for the indication. If varices are present both in the inferior segment of the esophagus and in the gastric fundus but are not connected, they are designated Lei, Lgf. D 0.3–5.0: The D plus diameter value is used to indicate the maximum diameter of the observed varicose veins. The diameter value is based on the selection of the following endoscopic treatment approaches: D0.3, D1.0, D1.5, D2.0, and D3.0. Rf 0, 1, 2: This indicates the risk of variceal bleeding of the observed veins. The Rfs associated with variceal bleeding mainly includes the following: (1) RC—a positive red color sign (RC+) refers to changes such as erythema, red streaks, and blood blisters on the surface of the variceal veins, which indicate risky varices; (2) HVPG—used to determine the occurrence and prognosis of GOV; (3) erosion—the superficial mucosa of varicose veins is damaged, which is a sign of

recent bleeding, and requires timely endoscopic treatment; (4) thrombus head: it is a sign of imminent bleeding and requires timely endoscopic treatment, whether it is red or white; (5) active bleeding: spurting or oozing from varicose veins can be observed on endoscopy; and (6) none of these factors are present, but fresh blood can be detected under the microscope, and nonvariceal bleeding factors can be ruled out. Depending on whether there are signs of recent bleeding and indications for emergency endoscopic treatment, it is divided into the following three gradients: (1) Rf 0: Rfs (1) to (5) and signs of recent bleeding are absent; (2) Rf 1: RC+ or an HVPG of more than 12 mmHg, with signs of recent bleeding and a need for endoscopic treatment; (3) Rf 2: erosion, thrombus head, and active bleeding are notable, and timely endoscopic treatment is required.

GOV can also be divided into three grades, mild, moderate, and severe, according to the shape of the varicose veins, the presence or absence of RC, and the risk of bleeding. The mild grade (G1) refers to GOV that is straight or slightly tortuous, without RC. The moderate grade (G2) refers to GOV that is straight or slightly tortuous and RC+ or GOV with serpentine or tortuous bulges but without an RC. The severe grade (G3) refers to GOV with serpentine or tortuous bulges that is RC+ or GOV that is beady, nodular, or tumor-like (regardless of the presence or absence of RC).[2,23]

Recommendation 1: Cirrhosis can be classified into compensated stage, decompensated stage, recompensated stage, and/or cirrhosis reversion (B1). The LSM combined with platelet count and multislice contrast-enhanced CT can be used as noninvasive examinations for the diagnosis of portal hypertension in cirrhosis. (B1)
Recommendation 2: Gastroscopy is the gold standard for the diagnosis of GOV and EVB. It is suggested to use gastroscopy combined with the noninvasive examination results to confirm the presence of GOV and assess severity in cirrhotic patients (A1). GOV should be graded into mild, moderate, and severe, and be recorded with sites, diameter, and Rfs for bleeding, etc.
Recommendation 3: It is recommended that cirrhotic patients with CSPH but without GOV should be followed up with gastroscope examination every two years, with once a year being acceptable for mild GOV (C1).
Recommendation 4: When CSPH is identified through noninvasive examinations, and portal hypertension in cirrhosis is diagnosed using multislice contrast-enhanced CT and gastroscopy, invasive HVPG detection is not recommended for the sole purpose of confirming the presence of CSPH (B1). HVPG>5 mmHg indicates portal hypertension; HVPG>10 mmHg suggests the possibility of developing varicose veins; HVPG>12 mmHg may suggest the possibility of the occurrence EVB, and HVPG>20 mmHg indicates a poor prognosis (A1).

Primary prevention of EVB

EVB management strategies include the (1) prevention of primary EVB (primary prevention); (2) control of acute esophageal-gastric variceal bleeding (AEVB); (3) prevention of re-EVB (secondary prevention); and (4) improvement of hepatic functional reserve. The purpose of primary prevention of EVB is achieved by treating the primary liver disease, preventing fibrosis, preventing the formation and progression of variceal veins, preventing moderate-to-severe variceal bleeding, and preventing the occurrence of complications.

Etiological treatment

Liver cirrhosis can be attributed to viruses, alcoholic liver disease, fatty liver disease, cholestatic disease, autoimmune hepatitis, genetic metabolic disease, drug-induced liver diseases, and parasitic diseases, and the treatment of the primary disease should be the focus. Hepatitis B is the main cause of liver cirrhosis in China. Antiviral therapy can alleviate liver fibrosis and reduce portal pressure, thus preventing the occurrence of varicose veins or bleeding and reducing the occurrence of end-stage liver disease and liver cancer. Liver diseases due to other causes should also be actively treated with a focus on their primary diseases to prevent the progression of liver cirrhosis.[24–32]

Anti-inflammatory and antihepatic fibrosis therapy

Anti-inflammatory and antihepatic fibrosis therapy may be considered in patients whose etiologies cannot be treated or whose liver inflammation and/or liver fibrosis persists or progresses despite adequate etiological treatment.[33] Currently, there is no Western treatment for hepatic fibrosis that has been clinically validated, and TCM has played an essential role.[34,35] In TCM, the basic pathogenesis of liver fibrosis is primary asthenia-secondary asthenia syndrome, and the main treatment principles are to promote blood circulation and remove blood stasis, to strengthen the body's resistance and tonify the body to compensate for deficiencies, to clear heat (via detoxification), and to remove dampness. Currently, commonly used antihepatic fibrosis drugs include Anlo Huaxian, Fuzheng Huayu, and Fufang Biejia Ruangan medicines. The prescription composition prescriptions reflect the principle of strengthening the alleviating factors and eliminating pathogenic factors and of treating both symptoms as well as underlying causes. The effects of the drugs are improved when administered on the basis of the differentiation of the TCM syndrome. Anlo Huaxian pills can enhance matrix metalloproteinase (MMP)-13 and inhibit MMP-2 and tissue inhibitors of metalloproteinases (TIMP)-1/2 expression in CCl4-induced liver fibrosis in rat models; upregulate peroxisome proliferator-activated receptor (PPAR)-γ and downregulate cytokines such as nuclear factor kappa B (NFκB); and play an antifibrotic role by inhibiting the profibrotic cytokine transforming growth factor (TGF)-β1, and the Smads signaling pathway.[36] Clinical studies have found that concomitant administration of these drugs in patients with chronic hepatitis B and liver cirrhosis on antiviral therapy can further reduce liver fibrosis and cirrhosis.[8,37–39]

In primary prevention, AEVB control, and secondary prevention strategies, attention should be paid to the patient's albumin level, and human serum albumin should be supplemented in time to promote wound healing, indirectly improve the hemostatic effect and reduce the occurrence of infection. Bacterial infection is a key factor leading to rebleeding in patients with liver cirrhosis, and albumin can control the risk of bleeding by promoting the transport of important drugs, such as proton pump inhibitors and antibiotics.[40] In addition, albumin regulates the osmotic pressure of the blood and intercellular space, maintains fluid balance, acts as an antioxidant by scavenging free radicals, and protects the integrity of the capillary endothelium. Antibiotic combinations are superior to single antibiotics in controlling inflammation and hemostasis in cirrhosis.[41]

Preventive measures for different degrees of varicose veins

Absence of esophageal varices: Main interventions include etiological treatment, anti-inflammation, liver protec-

tion, and antihepatic fibrosis. Studies have shown that nonselective beta-blockers (NSBBs) are unhelpful to prevent the development of esophageal varices in patients without esophageal varices.

Mild esophageal varices: Whether NSBBs should be used in patients with relatively mild esophageal varices is controversial.[42] Therefore, NSBBs are recommended only for patients with mild esophageal varices who are at an increased risk of bleeding.

Moderate-to-severe esophageal varices: The main pharmaceutical interventions include carvedilol, an NSBB that also blocks α1 receptors and can reduce liver vascular tone and resistance. Studies have confirmed that carvedilol, a new drug for preventing portal hypertension, can reduce HVPG by up to 20%, which is significantly higher than the effect of propranolol.[43] When NSBBs are applied to moderate and severe esophageal varices, the risk of primary bleeding in the treatment group is significantly lower than that in the control group, and the mortality rate is also significantly lower. Compared with endoscopic variceal ligation (EVL), the preventive effect is comparable.[44] NSBBs reduce portal pressure by reducing cardiac output, constricting splanchnic vessels, reducing bacterial translocation, and reducing the appearance of ascites and spontaneous bacterial peritonitis (SBP).[45]

Simvastatin increases the nitric oxide content in the liver, thus reducing HVPG in patients with cirrhosis without affecting systemic hemodynamic stability.[46] The effect of simvastatin in reducing HVPG can be superimposed on that of NSBB, but its long-term efficacy and safety should be investigated in studies with a larger sample size. There were no statistically significant differences in survival rates between nitrates alone and NSBB alone, nitrates combined with NSBB, and placebo. In some clinical trials, the risk of bleeding with nitrates alone was higher than that with placebo,[47] and it has more adverse reactions, so we do not recommend administering nitrates alone or in combination with NSBB.

An increased level of angiotensin II in patients with liver cirrhosis can lead to an increase in portal pressure,[48] but the application of angiotensin receptor blocker (ARB) in patients with portal hypertension did not achieve good efficacy. The addition of losartan to propranolol did not increase the decline of HVPG. Angiotensin converting enzyme inhibitors (ACEIs) and ARB have similar effects, but the main adverse reactions of ACEI/ARB are hypotension and renal failure. Therefore, ACEI/ARBs are currently not recommended for the treatment of portal hypertension.[49]

Spironolactone can also reduce portal pressure by reducing blood volume and splanchnic blood flow. Spironolactone alone or in combination with NSBB can reduce the risk of bleeding in patients with liver cirrhosis, but it has no significant effect on reducing mortality, and the incidence of adverse events is significantly increased. Therefore, spironolactone is not recommended for use alone or in combination with NSBB.[50]

Endoscopy: EVL has a good effect on preventing primary esophageal variceal bleeding. Some studies have compared the primary prevention effects of EVL and NSBB, showing that the two do not have statistically significant difference regarding the rate of gastrointestinal bleeding, mortality, and bleeding-related mortality.[51]

Endoscopy combined with drugs: Drugs combined with EVL are not more effective than drugs alone or EVL, and they increase the incidence of adverse events. Studies have shown that the combination therapy group had no advantages in reducing the rate of primary esophageal variceal bleeding, while the incidence of adverse events increased significantly.[52]

Portosystemic shunt and devascularization operation: Portosystemic shunt and devascularization operation reduce both the pressure of the portal vein and the risk of primary bleeding, but the incidence of HE increases significantly.[51] TIPS and shunt surgery have similar principles, so neither is indicated as an intervention to prevent initial bleeding.

Primary prevention of gastric variceal bleeding: There are relatively few studies on the primary prevention of gastric variceal bleeding. Type GOV1Leg is an extension of esophageal varices, and the current primary prevention measures are the same as those for esophageal varices. A previous study[53] has suggested that the rate of gastric variceal bleeding was significantly lower in the tissue adhesive group than in the and no treatment groups, and the tissue adhesive group also had a higher survival rate than the nontreatment group. The main adverse events of tissue adhesive injection are ectopic embolism and infection. The safety and efficacy of tissue adhesive injection in patients with gastric varicose veins needs further research, and NSBB is still advocated for these patients.

Monitoring liver cancer

Patients with liver cirrhosis are at an increased risk of developing liver cancer,[54] and routine screening (alpha-fetoprotein [AFP] and abdominal ultrasound) should be performed every 3–6 months; enhanced screening should be performed every 12 months (AFP, AFP-L3, protein induced by vitamin K deficiency or vitamin K antagonist-II protein (PIVKA) plus CT or magnetic resonance imaging [commonly known as MRI]) in patients who are at very high risk of liver cancer; precancerous lesions should be routinely examined every 1–3 months; and enhanced screening should be carried out every 6–12 months. Special examinations such as liver biopsy, liquid biopsy, and gadoxetate disodium (Gd-EOB-DTPA) enhanced MRI can be performed to improve the detection rate of early-stage liver cancer, as applicable..

Recommendation 5: EVB management strategies include (1) prevention of the first EVB (primary prevention); (2) control of AEVB; (3) prevention of the second EVB (secondary prevention); and (4) improvement of liver functional reserve (A1).
Recommendation 6: Attention should be paid to etiological treatment, as well as antiviral therapy and antihepatic fibrosis treatment (A1). TCMs such as Anluo Huaxian pills, Fuzheng Huayu capsules, and Fufang Biejia Ruangan tablets can be used to relieve liver fibrosis, liver cirrhosis, and GOV (B1).
Recommendation 7: In primary prevention, control of AEVB, and secondary prevention of liver cirrhosis, attention should be paid to serum albumin level of the patients, with timely supplementation of human serum albumin if necessary (B1).
Recommendation 8: NSBB is not recommended for primary prevention in patients without GOV (B1).
Recommendation 9: For mild GOV patients with Child-Pugh B and C, or positive RC sign, NSBB is recommended to prevent the first variceal bleeding (B1). In patients with mild GOV at low risk of bleeding, NSBB is not recommended (B2). For patients with mild GOV without NSBB, gastroscopy should be reviewed regularly (B1).
Recommendation 10: For patients with moderate or severe GOV and relatively high risk of bleeding (Child-

Pugh B, C, or positive RC sign), NSBB or EVL is recommended to prevent the first variceal bleeding (A1). For those at low risk of bleeding, NSBB is the first-line choice. EVL is alternative for patients with contraindications or intolerance to NSBB or poor compliance (B2).
Recommendation 11: The initial dose of carvedilol is 6.25 mg/d, which can be increased to 12.5 mg after 1 week if the prior dose was well tolerated; the initial dose of propranolol is 10 mg twice a day, which can be gradually increased to the maximum tolerated dose; and the initial dose of nadolol is 20 mg per day, followed by escalation to a maximum tolerated dose. Response criteria: the resting heart rate decreased to 75% of basal heart rate or 50–60 beats/m (A1); HVPG ≤12 mmHg or decreased ≥10% from baseline (B2).
Recommendation 12: Nitrates alone or in combination with NSBB are not recommended for primary prevention (A2). ACEI/ARB drugs are not recommended for primary prevention (B2). Spironolactone is not recommended for primary prevention (C2).
Recommendation 13: Surgical procedures and TIPS are not recommended for primary prevention (A2). Concomitant use of EVL and NSBB for primary prevention is not recommended (C2).
Recommendation 14: NSBB can be used for primary prevention of gastric variceal bleeding (B2).
Recommendation 15: LDRf classification should be used to guide patient monitoring and timing of treatment. Rf 0, D0.3: (primary prevention) No treatment, follow-up with endoscopy once a year. D1.0: Elective EVL or follow-up with endoscopy every half year (B1). D1.5: Elective endoscopic injection sclerotherapy (EIS) for esophageal varices plus tissue glue injection for gastric cardia, or endoscopy every 3 months to half a year; tissue glue injection for varices located outside the esophagus or endoscopy every 3 months to half a year (C2). Rf 1, treatment in 3 months

Treatment of AEVB

AEVB in liver cirrhosis is a common clinical critical illness involving multiple disciplines. Therefore, clinicians should comprehensively consider the patient's situation, diagnosis and treatment provided by the hospital's multidisciplinary collaborative team, and technical skill level of physicians when treating patients with AEVB with liver cirrhosis. The primary goal is to reduce the rate of mortality and improve the rate of hemostatic success.

Basic concepts

Diagnosis of AEVB: AEVB is considered an acute bleeding over a period of less than 5 days, and gastroscopy within 12–24 h is a reliable method of diagnosing AEVB. Active variceal bleeding (oozing and spurting), thrombus head, or the presence of varicose veins without other lesions that could explain the bleeding can be observed by endoscopy.[21]

Nonresponse/failure of EVB treatment: One of the following manifestations: (1) vomiting of fresh blood or aspiration of more than 100 mL of fresh blood by nasogastric tube ≥2 h after drug therapy or endoscopic therapy; (2) hemorrhagic shock; and (3) hemoglobin reduced by 30 g/L (hematocrit decreased by approximately 9%) in the absence of blood transfusion over any 24 h period.

Signs of rebleeding of EVB: Recurrent clinically significant active bleeding events after bleeding control (hematemesis, melena, or blood in the stool; systolic blood pressure decreases by >20 mmHg or heart rate increases by >20 beats/m; hemoglobin decreases by >30 g/L in the absence of blood transfusion). (1) Early rebleeding: AEVB occurs within 120 h to 6 weeks after the control of bleeding and (2) delayed rebleeding: AEVB occurs 6 weeks after the control of bleeding; non-EVB patients are not included.

Early treatment

Processing principle: Main interventions include correction for hypovolemic shock, effective control of bleeding, prevention of bleeding-related complications (such as infection, electrolyte and acid-base imbalance, and HE), maintenance of airway patency, oxygen inhalation, and monitoring of vital signs and urine output. Intensive care unit (ICU) admission is recommended for patients with massive bleeding or unstable vital signs. Patients with a small amount of bleeding and stable vital signs can be diagnosed, treated, and observed in the general ward.

Restrictive fluid resuscitation: Establishment of effective venous access (at least two) for rapid fluid rehydration and blood transfusion, and determination of volume expansion and fluid properties according to the degree of bleeding are required. A hemoglobin level greater than 60–70 g/L should be maintained by blood transfusion, and other factors, such as cardiovascular disease, age, and continuous bleeding, should be considered. Generally, blood transfusions can be required when hemoglobin is <70 g/L, and blood transfusion management practices must be followed.[55,56] Excessive volume expansion with plasma or blood transfusion cannot correct coagulation dysfunction and may lead to volume overload and aggravate portal hypertension-related complications. Rehydration with saline solution alone should be avoided, as it can exacerbate ascites or fluid retention at other extravascular sites. Indications for effective recovery of blood volume: (1) systolic blood pressure 90–120 mmHg; (2) pulse <100 beats/m; (3) urine output >17 mL/h; and (4) clinical manifestations—clear mind/improved mental state, without significantly dehydrated appearance.

Endoscopy and timing of treatment: Emergency endoscopy is defined as an endoscopic examination performed within 12 h of arrival at the hospital (emergency) by the European Society of Gastrointestinal Endoscopy. Early endoscopy and delayed endoscopy are defined as endoscopies between 12 and 24 h and >24 h of admission, respectively.[57] However, different guidelines have inconsistent recommendations for the timing of endoscopic diagnosis and treatment in patients with liver cirrhosis. Baveno VII recommends that patients with signs of cirrhosis should undergo endoscopy within 12 h of upper gastrointestinal bleeding after hemodynamic recovery. A multicenter prospective observational study from Europe and Canada enrolled 2,138 patients with AEVB and cirrhosis and found that endoscopic examination within 6 h or between 6 and 12 h, compared with that between 12 and 24 h, was not associated with reduced mortality.[58] In recent years, with the improvement of endoscopic treatment technology and experience, endoscopy and treatment can still be performed under general anesthesia with intubation and ICU support to save the lives of patients with refractory hemorrhagic shock or HE; this requires a collaborative multidisciplinary diagnosis and treatment team for AEVB in liver cirrhosis and the patients' families to be understanding and knowledgeable.[59]

Drug treatment

Once AEVB is suspected in cirrhosis, early administration of portal pressure reducing drugs and antibiotics are the pri-

mary treatment options.

Portal pressure reducing drugs: Commonly used clinical drugs to reduce portal venous pressure include terlipressin, somatostatin, and octreotide.[60] Vasopressin, including pituitrin, has rarely been used in the treatment of liver cirrhosis with AEVB owing to its short biological half-life, limited efficacy, and serious side effects. Although NSBB is effective in lowering portal pressure, it can lower blood pressure and inhibit cardiac pump function, and there are risks associated with the use of NSBB during the AEVB phase.

Terlipressin: It is also called triglycyl-lysine vasopressin (glypressin), which is a synthetic sustained-release agent of vasopressin, and its adverse reactions are less severe and milder than those of vasopressin. Terlipressin acts on the vascular V1 receptor, causing splanchnic vasoconstriction, alleviating the state of hyperdynamic splanchnic circulation, and reducing blood flow from the azygos vein and collateral circulation. A meta-analysis has shown that compared with the absence of a vasoactive drug, terlipressin improves the rate of bleeding control in 48 h and decreases in-hospital mortality.[61] Terlipressin reduced 30-day rebleeding and blood transfusion requirements significantly more than the Sengstaken-Blakemore tube.[61] Therefore, guidelines and studies[2,3] in China and other countries recommend terlipressin as the first-line drug to control AEVB at a dose of 2–12 mg/d, and continuous intravenous infusion may be more effective than intermittent bolus injection and has fewer adverse reactions.[62] The general course of treatment is 3–5 days, and the success rate of hemostasis is approximately 85%. Terlipressin combined with EVL can improve the hemostatic effect. Terlipressin can cause hyponatremia, so serum sodium levels should be monitored, especially in patients with poor liver function.

Somatostatin and octreotide: The half-life of somatostatin is 3–5 m, and the synthetic octapeptide somatostatin, octreotide, has a half-life of 70–90 m. Somatostatin reduces portal pressure by selectively constricting splanchnic blood vessels and reducing intrahepatic vascular resistance and portal blood flow. A continuous intravenous infusion of somatostatin at a rate of 250–500 μg/h or of octreotide at a rate of 25–50 μg/h has less adverse reactions. The general course of treatment is 3–5 days, and the bleeding control rate in the primary bleeding episode is approximately 80%. Clinical studies have shown that terlipressin, somatostatin, or octreotide have a similar efficacy in the control of AEVB in cirrhosis. Terlipressin can be used as an alternative to or in addition to conventional therapy in patients who failed somatostatin or octreotide therapy.

Antibacterial drugs: In patients with active gastrointestinal bleeding from liver cirrhosis, inflammation and edema of the gastrointestinal mucosa and bacterial translocation are often present, and bacterial infection occurs within 48 h in approximately 20% of patients.[63] In patients with Child-Pugh A cirrhosis, the risk of bacterial infection and death is extremely low, and prospective studies are needed to evaluate the risks and benefits of prophylactic antibiotics. Patients with Child-Pugh class C or with diabetes or liver cancer are susceptible to infection, and early rebleeding and mortality are associated with uncontrolled bacterial infection. Studies have shown that antibacterial drugs are an indispensable intervention for the treatment of AEVB in cirrhosis. Prophylactic intravenous administration of broad-spectrum antibacterial drugs 8 h before endoscopy can reduce the occurrence of bacteremia and SBP. Third generation cephalosporins are preferred, especially in patients who have received quinolones in the past. For drug selection, refer to the Guidelines for the Clinical Application of Antimicrobial Agents (2021 edition). Ceftriaxone at a dose of 1–2 g/d can be used for a course of 3–5 days. If there is evidence of infection, it should be considered to prolong the course of treatment. Despite antimicrobial prophylaxis, bacterial infections persist in 20% of patients with AEVB, the most common of which are respiratory infections and SBP.[64]

Proton pump inhibitors: The success rate of gastrointestinal bleeding hemostasis can be improved if the pH of the gastric juice is >5. There are various proton pump inhibitors (PPIs), including omeprazole and pantoprazole. An intravenous bolus injection of PPIs at a dose of 40–80 mg/d or continuous intravenous infusion of PPI at a rate of 8 mg/h for 5–7 days can be administered. A meta-analysis[65] found that PPI administration for more than 1 month could reduce the rate of rebleeding after gastroscopic treatment in patients with AEVB of liver cirrhosis, but it was not associated with bleeding-related mortality. Long-term use of PPIs can cause intestinal bacterial translocation and increase the incidence of SBP in patients with liver cirrhosis.[66] Therefore, PPIs should be discontinued after gastroscopy in patients who have used PPIs before gastroscopic examination and have no indication of peptic ulcer.

Other drugs: There is insufficient evidence for definitive treatment outcomes of topical application of cold saline containing noradrenaline (0.9% isotonic saline 100 mL with 8 mg of noradrenaline), oral Yunnan Baiyao and thrombin, intravenous injection of hemocoagulase, or vitamin K1 in the treatment of AEVB in cirrhosis. Therefore, the frequent use of these hemostatic agents should be avoided.[67,68] For patients with cirrhosis and anemia, especially those who may undergo invasive surgery, hemoglobin levels can increase with iron, folic acid, vitamin B6, and vitamin B12 supplementation, and prophylactic blood transfusions are not recommended.

Malnutrition increases the risk of adverse outcomes in cirrhosis patients with AEVB.[69] Generally, oral food intake and nutritional preparations can be initiated 24 h after active bleeding is controlled. Early oral food intake does not increase the risk of rebleeding.[70,71] Oral administration of lactulose or enema can promote intestinal blood discharge, which is beneficial for preventing and treating liver encephalopathy.

Gastroscopy

Currently, gastroscopic therapy remains the main intervention for AEVB in cirrhosis. Its purpose is to control acute bleeding and eradicate varicose veins or minimize them as much as possible to prevent rebleeding. Gastroscopic treatment procedures include EVL, EIS, and endoscopic clipping or tissue adhesive (tissue glue) injection therapy. Hemodynamically stable or recovered AEVB patients with suspected cirrhosis should undergo a gastroscopy in 12–24 h.

EVL: EVL is indicated for patients with LDRf type D1.0-D2.0 esophageal varices and patients with GOV1 EVB or AEVB who had received surgery, vascular, and other interventions. When the diameter of the variceal vein is greater than 2.0 cm, the risk of recent major bleeding after EVL is increased. A 6 or 7 multiband ligator is commonly used, and ligation can be repeated or sclerotherapy injection and other sequential treatments can be performed 2–4 weeks after the first ligation until all varicose veins disappear or generally disappear.

EIS: (1) The indications are the same as those of EVL. For patients with esophageal varices who are not eligible for EVL treatment, EIS can be used; its treatment efficacy is similar to that of EVL in controlling bleeding but with a much higher complication rate of esophageal ulcers and strictures after the procedure.[72] (2) After the first EIS, EIS or EVL can be repeated at intervals of 2–4 weeks until the varicose veins have been eradicated or are generally eradicated. A com-

monly used sclerosing agent is polidocanol (10 mL:100 mg). Intravenous injection for varicose veins is also used. One to four sites are injected each time; the initial injection volume is preferably approximately 10 mL per site, and the total amount is generally not greater than 40 mL per injection. Dosage can be reduced or increased depending on the severity of the varicose veins. In addition, 5% sodium morrhuate has been used rarely clinically owing to its side effects.

Gastroscopic tissue adhesive injection: It is preferable for isolated gastric varices (IGV) and gastric varices type II (GOV2) bleeding classified according to the Sarin classification.[73] Commonly applied tissue adhesives include n-butyl cyanoacrylate, whose intravenous injection is administered via the sandwich technique. Polidocanol or hypertonic glucose can be used, while lipiodol administration is not recommended via the sandwich technique. Generally, the varicose vein should be completely occluded after one injection. The injection dose is estimated according to the severity of the gastric varices, and treatment can be repeated if the effect is not satisfactory until the gastric varices have been occluded.[74] Injection of thrombin through gastroscopy in the treatment of gastric varices bleeding has achieved good outcomes, with an early rebleeding rate of 9.3%; a late rebleeding rate of 13.8%; and a 6-week gastric varices-related mortality rate of 7.6%. These were similar to those of the tissue adhesive group; however, the adverse event rate was 5.6%, which was significantly lower than that of the tissue adhesive group.[75]

Injection of tissue adhesive with EUS guidance: The indications are the same as those of tissue adhesive injection using a gastroscope. A meta-analysis of tissue adhesive injection under EUS while treating gastric varices (n = 851) showed that the occlusion rate of gastric varices was 84.4%, recurrence rate was 9.1%, early rebleeding rate was 7.0%, and late rebleeding rate was 11.6%. Therefore, it was superior to direct injection using the gastroscope.[76]

Drug-assisted endoscopic therapy: Portal pressure reducing agents can significantly reduce HVPG, improve the safety and efficacy of endoscopic therapy, and reduce recent rebleeding.[77] Terlipressin or octreotide as an adjuvant to EVL leads to a hemostasis rate of 98% and 96%, respectively; Rebleeding rates at 5 days and 42 days were 12%/9% and 28%/24%, respectively; There were no significant differences between the two groups. Routine use of the prothrombin complex, fresh frozen plasma, and fibrinogen is not recommended to reduce the incidence of bleeding related to endoscopic therapy to avoid portal vein thrombosis.

Fully covered self-expandable esophageal metal stent (SEMS): After drug or gastroscopic treatment, 15–20% of patients still experience recurrent or active bleeding that cannot be effectively controlled; endoscopic SEMS salvage therapy is effective when the life of the patient is seriously threatened and other salvage interventions (such as TIPS or surgery) are unavailable.[78]

Contraindications to endoscopic therapy: Absolute contraindications: (1) those with contraindications to gastrointestinal endoscopy; (2) the patient did not sign the informed consent; and (3) refractory disseminated intravascular coagulation or multiple organ failure. Relative contraindications: (1) uncontrolled HE or hemorrhagic shock and (2) severe liver and kidney dysfunction and massive ascites.

Sengstaken-Blakemore tube compression for hemostasis

In the absence of favorable drug treatment effects, emergency gastroscopy, and TIPS treatment, Sengstaken-Blakemore tube compression can be applied as a temporary rescue intervention.[79] The success rate for hemostasis is 80–90%, but the rate of rebleeding is as high as 50%. In addition, patients experience great pain and have many complications, such as pneumonia by aspiration and esophageal rupture. Sengstaken-Blakemore tube compression cannot be used in patients who are in a deep coma, cannot cooperate with the operation, refuse to sign informed consent, or have a history of esophageal surgery.

TIPS

TIPS is one of the key interventions to reduce portal resistance structurally and significantly in a minimally invasive manner by establishing a shunt channel within the liver parenchyma between the hepatic vein and the portal vein, usually punctured through the jugular vein. The advantage of TIPS is that it is minimally invasive, and that successful surgery can produce positive immediate outcomes; however, there are risks of restenosis or occlusion of the shunt, impaired liver function, and postoperative HE.[80,81] The application of polytetrafluoroethylene-covered stents significantly reduces complications such as restenosis or occlusion and thrombosis after TIPS. Current evidence suggests that TIPS can act as salvage therapy for patients who have failed medical and/or gastroscopic therapy. Additionally, TIPS treatment can be performed as soon as possible for (1) Child-Pugh C (<14 points); (2) Child-Pugh B cirrhosis and EVB by gastroscopy; and (3) those with a HVPG>20 mmHg and other high-Rfs—that is, early TIPS (also referred to as eTIPS) (within 72 h) or pre-emptive TIPS (also referred to as pTIPS).

In patients with cirrhotic AEVB with end-stage liver disease or acute-on-chronic liver failure (ACLF), pTIPS improves liver transplant-free survival.[82] Therefore, HE and hyperbilirubinemia in AEVB patients with ACLF at admission are not absolute contraindications to TIPS. For patients with GOV2 and IGV1 who had acute bleeding, TIPS combined with gastric coronary vein embolization can reduce the risk of early rebleeding of the gastric varices and improve the hemostatic effect.

Transvenous retrograde balloon catheter embolization

Balloon-occluded retrograde transvenous obliteration (BRTO) is a procedure that uses a balloon catheter to occlude abnormal shunts, such as gastrorenal shunts; sclerosing agents and/or coils are injected to embolize varicose gastric veins to control gastric variceal bleeding.[83] BRTO is indicated for patients with GOV2, IGV1, and variceal bleeding at rare sites, especially in patients with or at high risk of HE, and is an alternative to gastroscopic therapy or TIPS. A study comparing the efficacy and safety of gastroscopic tissue adhesive and BRTO in the treatment of gastric varices in cirrhotic patients found that the rate of rebleeding in the gastroscopic treatment group was higher than that of BRTO. The 1-year and 2-year rebleeding-free rates were 77%/96.3% and 65.2%/92.6%, respectively, but the 2-year survival rates and complication rates were similar.[84]

Splenectomy and/or pericardial devascularization (devascularization)

Splenectomy is indicated in patients with Child-Pugh A/B cirrhosis and AEVB or with uncontrolled bleeding that does not respond to drug therapy or gastroscopic treatment when emergency TIPS is unavailable; emergency devascularization can save their lives. For those with Child-Pugh C, liver transplantation is preferred.[85] The incidence of portal vein thrombosis (PVT) after splenectomy is as high as approximately 50%, and PVT affects the recovery of portal hypertension and

subsequent treatment interventions, such as TIPS or liver transplantation. Therefore, splenectomy should only be used as a salvage intervention in a setting of failure of medical and gastroscopic therapies or in the absence of emergency TIPS.

Refractory EVB

Refractory patients with EVB are generally those who have active EVB within 5 days after drug or/and endoscopic therapy. It is more common in patients with Child-Pugh class C or ACLF or in patients with HVPG>20 mmHg.[81] For patients with liver cirrhosis with refractory EVB, TIPS or liver transplantation is necessary based on their technical advantages characterized by the multidisciplinary collaborative diagnostic and treatment team for liver cirrhosis and portal hypertension in each hospital. Patients with ACLF receive higher priority for liver transplantation on the waiting list.[86]

Recommendation 16: Drugs are the preferred treatment for EVB (A1). The vasoactive drug terlipressin (maintain on 2–12 mg/d infusion), somatostatin (250–500 μg/h), or octreotide (25–50 μg/h) are the first-line treatment drugs for AEVB, and the treatment duration is 3–5 days (A1).
Recommendation 17: Antibiotics are important therapeutic drugs of AEVB in cirrhosis, which can reduce the incidence of recurrent bleeding and bleeding-related mortality in esophagogastric varices(A1).
Recommendation 18: EVL and EIS can be used in patients with esophageal varicose veins and type GOV1 EVB (A1); tissue adhesive injection is indicated for GOV2 and IGV variceal bleeding (A1).
Recommendation 19: Terlipressin, somatostatin, and octreotide, in combination with endoscopic therapy, can improve the safety and efficacy of endoscopic therapy, reduce the incidence of recent recurrent bleeding after endoscopic therapy (A1).
Recommendation 20: For patients who do not respond to therapeutic drugs, early endoscopic or vascular interventional therapy should be implemented according to the conditions of the hospital and experiences of multidisciplinary team(B1).
Recommendation 21: Compression hemostasis with a Sengstaken-Blakemore tube can be used as a temporary transition therapy for patients who do not respond to drugs or endoscopic therapy when emergency endoscopic/TIPS therapy (B1) is not available.
Recommendation 22: Anesthesia intubation and ICU support can improve the efficacy and safety of the emergent endoscopic treatment of EVB (B1).
Recommendation 23: In patients with Child-Pugh A/B class, surgical devascularization is still an effective technique to control AEVB in patients who are unresponsive to drugs or endoscopic therapy when TIPS is not available (B1).

Secondary prevention of EVB

After controlling AEVB, patients still have a high risk of rebleeding and death. For patients who have not received secondary prevention, the rate of rebleeding within 1–2 years is as high as 60% and the mortality rate at 6 weeks is as high as 20%. Therefore, secondary prevention is very important to reduce rebleeding and GOV mortality in patients with cirrhosis. Secondary prevention procedures include NSBB, endoscopy, vascular intervention, and surgical treatment.[86,87] To date, systematic reviews and meta-analyses have failed to draw consistent conclusions about the efficacy and safety of these treatments.[88] Therefore, to ensure an optimal choice from these treatment methods, the technical advantages of the hospital's collaborative multidisciplinary diagnosis and treatment team must be taken into consideration; it is also necessary to carry out relevant multicenter, prospective, and high-quality clinical research.

Secondary prevention purpose

To eradicate or alleviate GOV, reduce the rate of rebleeding, and reduce mortality.

Timing of secondary prevention

Secondary prevention can start within 5 days after episodes of EVB or AEVB. Routine evaluation of liver reserve function and severity of portal hypertension is required prior to secondary prevention. Current studies have shown that Child-Pugh class C, PVT or tumor thrombus, severe varicose veins (>20 mm in diameter), or RC+ and blood blister sign positivity are high-Rfs for rebleeding from esophagogastric varices. HVPG>20 mmHg is a predictor of esophagogastric varices rebleeding and no response to drug or gastroscopic therapy.

Medical treatment

NSBB: Commonly used drugs are propranolol and carvedilol. Carvedilol prevents variceal rebleeding in patients with cirrhosis, the treatment effect of which is similar to that of EVL.[89] A randomized controlled study comparing the safety and efficacy of propranolol and carvedilol in the secondary prevention of rebleeding of the esophagogastric varices with a 6-year follow-up period found that the HVPG response of the carvedilol group was higher than that of the propranolol group (72% vs. 47.8%),[90] while the rates of rebleeding at 1 and 3 years were lower (8.9% and 24.0% in the carvedilol group vs. 16.0% and 36.7% in the propranolol group). New onset/worsening ascites was more common in propranolol-treated patients (69.5% vs. 40.0%). There were no significant differences in overall mortality, upper gastrointestinal bleeding, and adverse events, although carvedilol had a higher degree of HVPG response than propranolol.

Vasodilator: Nitrates, α2-receptor blockers, calcium ion blockers, and serotonin receptor blockers are included.[91,92] Most of the evidence derives from basic research, and there is little evidence and experience from clinical research. Although NSBB in combination with nitrates and EVL can prevent variceal esophageal rebleeding, nitrates can have adverse effects on acute kidney injury in patients with cirrhosis.[93] In conclusion, an ideal portal pressure reducing agent should have a highly selective effect on the splanchnic vascular bed, maintain effective blood perfusion in the liver, and improve liver function. Therefore, the search for novel drugs that can reduce portal venous pressure remains an urgent clinical problem to be solved.

Gastroscopy

The goal is to eradicate or significantly reduce GOV, rebleeding rates, and the associated mortality. In clinical practice, accurately predicting or assessing the risk of variceal bleeding or rebleeding in cirrhosis and reducing unnecessary endoscopic screening remain clinical challenges.[94]

Gastroscopy combined with NSBB therapy: NSBB can reduce HVPG in patients with cirrhotic portal hypertension and prevent rebleeding of GOV and decompensation of liver cirrhosis,[95,96] and endoscopic therapy can eradicate or alleviate

GOV.[97,98] The technique of endoscopic therapy is the same as that of AEVB. Compared with the use of EVL or NSBB alone, EVL combined with propranolol or carvedilol had a better effect in preventing rebleeding from GOV rebleeding and improves the long-term survival rate.[99] Therefore, gastroscopy combined with NSBB is the standard regimen for the secondary prevention of rebleeding from GOV unless the patient is intolerant to the drug. Patients who have already received NSBB for primary prevention require a combination with endoscopic therapy.[100,101] However, in patients with massive ascites, EVL alone is more suitable for the prevention of GOV rebleeding than EVL in combination with NSBB owing to the increased risk of adverse effects of NSBB and acute kidney injury.[102]

Sequential periodic therapy and long-term endoscopy monitoring: There is still no unified view on the optimal interval and cycle of gastroscopic therapy. Gastroscopy is usually performed 2–4 weeks after the initial treatment to evaluate the effect of the first treatment. If the GOV has not yet been eradicated or there is still a risk of rebleeding and the esophageal mucosal ulcer is completely healed, multiple cycles of EVL, EIS, or tissue adhesives can be repeated until the patient's GOV has been eradicated or there is no risk of rebleeding.[97,103] Endoscopy should be performed at least once every 12 months to assess the risk of recurrence of GOV after GOV eradication or when there is no risk of bleeding. For patients who have undergone a gastroscopic intervention, lifelong gastroscopic monitoring and follow-up is required for sequential gastroscopic treatment.

Vascular interventional therapy

TIPS and BRTO are the main approaches for vascular intervention in cirrhotic portal hypertension. TIPS is an option for rebleeding after NSBB and/or combined gastroscopy.[100,101] For patients with Child-Pugh A/B, TIPS or surgical devascularization may be considered when patients are unresponsive to endoscopy and medical therapy. BRTO can also be applied when BRTO indications are met. Owing to the popularization of gastroscopic treatment technology, other percutaneous transhepatic vascular intervention approaches, including percutaneous transhepatic and gastric coronary venous embolization, have rarely been performed clinically.

Liver transplantation

Liver transplantation is the ultimate treatment for patients with end-stage cirrhosis and ACLF, especially patients with refractory EVB.[101]

Recommendation 24: Endoscopy combined with NSBB is the standard regimen for secondary prevention of EVB. (A1) If patients are intolerant to combination therapy, monotherapy with either technique can be used for secondary prevention.
Recommendation 25: Gastroscopy should be performed 2–4 weeks after the initial endoscopic treatment to evaluate the effect of treatment. Multiple cycles of sequential treatment can be performed at intervals of 2–4 weeks, with GOV eradication or no risk of rebleeding as the end point of treatment. Endoscopy should be performed at least 12 months after eliminating or significantly reducing GOV to assess the risk of GOV recurrence and rebleeding (C1).
Recommendation 26: NSBB is not recommended in the primary or secondary prevention of EVB in patients with liver cirrhosis complicated by refractory ascites or acute kidney injury (B1).

Treatment of special types of varicose veins

Varicose veins at rare sites

Varicose veins at rare sites refer to those that are located in parts of the digestive system other than the esophagus and stomach, such as the duodenum, biliary tract, and bowel, or other systems other than the digestive system, such as the peritoneum and ovary. The 1-year all-cause mortality, MELD score, admission to the ICU, rates of octreotide and antibiotic use, and HVPG were significantly lower in patients with variceal hemorrhage at rare sites than in patients with AEVB with cirrhosis. EIS, EVL, tissue adhesive injection, and TIPS combined with embolization can be applied in case of variceal hemorrhage at rare sites.[104] Favorable efficacy and safety are only reported in some case reports, and multidisciplinary diagnosis and treatment are required.

PVT with cirrhosis EVB

In patients with liver cirrhosis and PVT treated with TIPS and anticoagulation therapy and in untreated patients, the early/late PVT improvement rate was 72%/78%, 27%/29%, and 10%/17%, respectively. No increase in bleeding complications from low molecular weight heparin anticoagulants was observed.[105] For patients with cirrhosis and PVT, both TIPS and low molecular weight heparin anticoagulants can be considered safe and effective interventions;[106] TIPS is more effective than EVL in combination with NSBB in preventing rebleeding and achieving recanalization of PVT in patients with Child-Pugh class A/B cirrhosis and PVT. The earlier the anticoagulation treatment with low molecular weight heparin, the higher the rate of recanalization of the portal vein. The recanalization rate was 69% when treatment was started in the first week; the recanalization rate decreased to 25% when treatment started in the second week. However, in patients with cirrhotic PVT and AEVB, the timing of initiation of anticoagulation remains inconclusive. For recently formed PVT, it is generally believed that the sooner anticoagulation therapy is initiated after active bleeding is controlled, the higher the rate of recanalization of PVT.

Portal vein tumor thrombus with EVB owing to liver cirrhosis

Approximately 85–90% of liver cancer cases occur owing to cirrhotic portal hypertension, and the management of AEVB and tumor thrombus remains a clinical conundrum. TIPS is an effective and safe technique to prevent rebleeding of the GOV in patients with liver cancer and portal hypertension. Compared with endoscopic therapy, TIPS significantly reduces the risk of rebleeding, but there is no difference in overall liver transplant-free survival between them.[107]

Recommendation 27: Tissue adhesive injection, EIS, EVL, and TIPS are effective treatment techniques for variceal bleeding at rare sites, which can be determined according to the patient's wishes and the technical advantages of a collaborative multidisciplinary team for diagnosis and treatment (C1).
Recommendation 28: For those who have complete or partial PVT (>50%) of the main portal vein, PVT involving the mesentery with the risk of bleeding of GOV, or symptomatic PVT or those who are on the waiting list for liver transplantation, low molecular weight heparin anticoagulation is recommended (B1).
Recommendation 29: For patients with cirrhosis with PVT and EVB, endoscopic therapy or TIPS can be used

to control acute bleeding. In the prevention of rebleeding, the treatment effect of TIPS is superior to that of endoscopic therapy (A1). Early initiation of anticoagulation therapy can improve the therapeutic effect of endoscopy or TIPS after bleeding has been controlled (B1).

Recommendation 30: For cirrhotic patients with EVB and portal vein tumor thrombus, endoscopic therapy or TIPS can be chosen to control acute bleeding and prevent recurrence (B1).

Problems to be addressed and prospects

(1) Related research on concepts and clinical diagnostic criteria for liver cirrhosis re-compensation and reversal of portal hypertension. (2) Development and clinical application of noninvasive measurement technology and biomarker risk stratification for portal pressure/HVPG in liver cirrhosis. (3) Noninvasive assessment methods for the severity of GOV in liver cirrhosis; efficacy and safety of NSBB and EVL in the primary prevention of EVB and the prevention of decompensation of liver cirrhosis; and development of novel drugs targeting the reduction of portal pressure. (4) Optimal therapeutic effect and safety evaluation of vasoactive drugs, NSBB, gastroscopic sequential therapy, and TIPS in AEVB; secondary prevention and decompensation of liver cirrhosis; cycle of gastroscopic sequential therapy; and timing of NSBB withdrawal. (5) In-depth study on the mechanism of action of TCM against liver fibrosis and cirrhosis. (6) Effects and evaluation of the effect of albumin, PVT, and platelet levels on EVB in liver cirrhosis and the progression of liver cirrhosis and timing, course of treatment, and efficacy and safety evaluation of low molecular weight heparin anticoagulation therapy

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References

[1] Chinese Society of Gastroenterology, Chinese Medical Association, Chinese Society of Hepatology, Chinese Medical Association, Chinese Society of Endoscopology, Chinese Medical Association. Consensus on prevention and treatment for gastroesophageal varices and variceal hemorrhage in liver cirrhosis. Zhonghua Gan Zang Bing Za Zhi 2008;16(8):564–570. Chinese. doi:10.3321/j.issn:1007-3418.2008.08.002.

[2] Chinese Society of Hepatologyf, Chinese Medical Association, Chinese Society of Gastroenterology, Chinese Medical Association, Chinese Society of Endoscopology, Chinese Medical Association. Guidelines for the diagnosis and treatment of esophageal and gastric variceal bleeding in cirrhotic portal hypertension. J Clin Hepatol 2016;32(2):203–219. Chinese. doi:10.3969/j.issn.1001-5256.2016.02.002.

[3] Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, *et al*. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–460. doi:10.1016/j.jhep.2018.03.024, PMID:29653741.

[4] Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, *et al*. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74(2):1014–1048. doi:10.1002/hep.31884, PMID:33942342.

[5] Aithal GP, Palaniyappan N, China L, Härmälä S, Macken L, Ryan JM, *et al*. Guidelines on the management of ascites in cirrhosis. Gut 2021;70(1):9–29. doi:10.1136/gutjnl-2020-321790, PMID:33067334.

[6] Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, *et al*. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015;64(11):1680–1704. doi:10.1136/gutjnl-2015-309262, PMID:25887380.

[7] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll V, Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–974. doi:10.1016/j.jhep.2021.12.022, PMID:35120736.

[8] Chinese Society of Hepatology,Chinese Medical Association. Chinese guidelines on the management of liver cirrhosis. Zhonghua Gan Zang Bing Za Zhi 2019;27(11):846–865. Chinese. doi:10.3760/cma.j.issn.1007-3418.2019.11.008, PMID:31941240.

[9] Hu Z, Li Y, Li C, Huang C, Ou Z, Guo J, *et al*. Using Ultrasonic Transient Elastometry (FibroScan) to Predict Esophageal Varices in Patients with Viral Liver Cirrhosis. Ultrasound Med Biol 2015;41(6):1530–1537. doi:10.1016/j.ultrasmedbio.2015.02.005, PMID:25817781.

[10] Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, *et al*. Noninvasive Diagnosis of Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease. Am J Gastroenterol 2021;116(4):723–732. doi:10.14309/ajg.0000000000000994, PMID:33982942.

[11] Chinese Foundation for Hepatitis Prevention and Control, Chinese Society of Infectious Disease and Chinese Society of Hepatology, Chinese Medical Association, Liver Disease Committee of Chinese Research Hospital Association. Consensus on clinical application of transient elastography detecting liver fibrosis: a 2018 update. Zhonghua Gan Zang Bing Za Zhi 2019;27(3):182–191. Chinese. doi:10.3760/cma.j.issn.1007-3418.2019.03.004, PMID:30929334.

[12] Li Y, Li L, Weng HL, Liebe R, Ding HG. Computed tomography vs liver stiffness measurement and magnetic resonance imaging in evaluating esophageal varices in cirrhotic patients: A systematic review and meta-analysis. World J Gastroenterol 2020;26(18):2247–2267. doi:10.3748/wjg.v26.i18.2247, PMID:32476790.

[13] Kim SH, Kim YJ, Lee JM, Choi KD, Chung YJ, Han JK, *et al*. Esophageal varices in patients with cirrhosis: multidetector CT esophagography—comparison with endoscopy. Radiology 2007;242(3):759–768. doi:10.1148/radiol.2423050784, PMID:17229872.

[14] Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, *et al*. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014;80(2):221–227. doi:10.1016/j.gie.2013.07.023, PMID:25034836.

[15] Hammoud GM, Ibdah JA. Utility of endoscopic ultrasound in patients with portal hypertension. World J Gastroenterol 2014;20(39):14230–14236. doi:10.3748/wjg.v20.i39.14230, PMID:25339809.

[16] Li M, Xu X. Researches on the prevention and treatment of bleeding gastroesophageal varices secondary to portal hypertension in patients with cirrhosis. Zhonghua Gan Zang Bing Za Zhi 2015;23(4):247–249. Chinese. doi:10.3760/cma.j.issn.1007-3418.2015.04.003, PMID:26427078.

[17] Morrison JD, Mendoza-Elias N, Lipnik AJ, Lokken RP, Bui JT, Ray CE Jr, *et al*. Gastric Varices Bleed at Lower Portosystemic Pressure Gradients than Esophageal Varices. J Vasc Interv Radiol 2018;29(5):636–641. doi:10.1016/j.jvir.2017.10.014, PMID:29352698.

[18] D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, *et al*. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39(10):1180–1193. doi:10.1111/apt.12721, PMID:24654740.

[19] de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–752. doi:10.1016/j.jhep.2015.05.022, PMID:26047908.

[20] Qi X, Dai J, Yang M, Ren W, Jia J, Guo X. Association between Portal Vein Thrombosis and Survival in Non-Liver-Transplant Patients with Liver Cirrhosis: A Systematic Review of the Literature. Gastroenterol Res Pract 2015;2015:480842. doi:10.1155/2015/480842, PMID:25810714.

[21] Asrani SK, Kamath PS. Prediction of early mortality after variceal bleeding: score one more for MELD. Gastroenterology 2014;146(2):337–339. doi:10.1053/j.gastro.2013.12.022, PMID:24361433.

[22] Linghu E. Notes on the Tentative guidelines for endoscopic diagnosis and treatment of varicosity and variceal bleeding in digestive tract (2009). Chin J Laparoscopic Surgery (Electronic Edition) 2011;4(5):331–333. Chinese. doi:10.3877/cma.j.issn.1674-6899.2011.05.003.

[23] Study Group of Gastroesophageal Varices, Chinese Society of Endoscopy, Chinese Medical Association. Tentative guidelines for endoscopic diagnosis and treatment of varicosity and variceal bleeding in digestive tract (2009). Chin J Dig Endosc 2010;27(01):1–4. Chinese. doi:10.3760/cma.j.issn.1007-5232.2010.01.001.

[24] Wang G, Duan Z. Guidelines for Prevention and Treatment of Chronic Hepatitis B. J Clin Transl Hepatol 2021;9(5):769–791. doi:10.14218/JCTH.2021.00209, PMID:34722192.

[25] Chinese Society of Hepatology, Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the prevention and treatment of hepatitis C (2019 version). Zhonghua Gan Zang Bing Za Zhi 2019;27(12):962–979. Chinese. doi:10.3760/cma.j.issn.1007-3418.2019.12.008, PMID:31941258.

[26] Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 2020;71(2):686–721. doi:10.1002/hep.31060, PMID:31816111.

[27] National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association, Fatty Liver Expert Committee, Chinese Medical Doctor Association. Guidelines of prevention and treatment for alcoholic liver disease: a 2018 update. Zhonghua Gan Zang Bing Za Zhi 2018;26(3):188–194. Chinese. doi:10.3760/cma.j.issn.1007-3418.2018.03.007, PMID:29804392.

[28] National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association, Fatty Liver Expert Committee, Chinese Medical Doctor Association. Guidelines of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update. Zhonghua Gan Zang Bing Za Zhi 2018;26(3):195–203. Chinese. doi:10.3760/cma.j.issn.1007-3418.2018.03.008, PMID:29804393.

[29] Chinese Society of Hepatology, Chinese Medical Association. Guidelines on the diagnosis and management of autoimmune hepatitis (2021). Zhonghua Gan Zang Bing Za Zhi 2022;30(5):482–492. Chinese. doi:10.3760/cma.j.cn112138-20211112-00796, PMID:35764540.

[30] You H, Duan W, Li S, Lv T, Chen S, Lu L, *et al*. Guidelines on the Diagnosis and Management of Primary Biliary Cholangitis (2021). J Clin Transl Hepatol 2023;11(3):736–746. doi:10.14218/JCTH.2022.00347, PMID:36969891.

[31] Chinese Society of Hepatology, Chinese Medical Association. Guidelines on the diagnosis and management of primary sclerosing cholangitis (2021). Zhonghua Gan Zang Bing Za Zhi 2022;30(2):169–189. Chinese. doi:10.3760/cma.j.cn112138-20211109-00786, PMID:35359068.

[32] Huang A, Liang QS, Sun Y, Zou ZS. Research progress in the diagnosis and treatment of chronic drug-induced liver injury. Infect Dis Info 2018;31(02):105–107. Chinese. doi:10.3969/j.issn.1007-8134.2018.02.003.

[33] Chinese Society of Infectious Diseases, Chinese Medical Association, Expert Committee for Prevention and Management of Liver Inflammation. Consensus statement by the expert committee for prevention and management of liver in China. Zhonghua Gan Zang Bing Za Zhi 2014;22(2):94–103. Chinese. doi:10.3760/cma.j.issn.1007-3418.2014.02.006, PMID:30704229.

[34] Liu YQ, Zhang C, Li JW, Cao LH, Zhang ZQ, Zhao WF, *et al*. An-Luo-Hua-Xian Pill Improves the Regression of Liver Fibrosis in Chronic Hepatitis B

Patients Treated with Entecavir. J Clin Transl Hepatol 2023;11(2):304–313. doi:10.14218/JCTH.2022.00091, PMID:36643032.
[35] Nan YM, Kong LL. Advances in diagnosis and treatment of liver cirrhosis with integrated traditional Chinese and Western medicine. Zhonghua Gan Zang Bing Za Zhi 2018;26(5):328–331. Chinese. doi:10.3760/cma.j.issn.1007-3418.2018.05.003, PMID:29996198.
[36] Wang L, Lu W, Gao Y, Cao X, Pei F, Liu X, *et al*. Effect of Anluohuaxianwan on the expression of matrix metalloproteinases and their inhibitors in rat liver with fibrosis. Zhonghua Gan Zang Bing Za Zhi 2019;27(4):267–273. Chinese. doi:10.3760/cma.j.issn.l007-3418.2019.04.006, PMID:31082337.
[37] Shi K, Liu Y, Wang X, Li Y, Zhang Q, Hu Y, *et al*. Adjuvant Fuzheng Huayu Capsule Reduces the Incidence of Hepatocellular Carcinoma in Patients with Hepatitis B-Caused Cirrhosis. Evid Based Complement Alternat Med 2020;2020:8826091. doi:10.1155/2020/8826091, PMID:33178324.
[38] Yang NH, Yang SL, Zhou YP, Yuan GS, Zhou YC, Liu JW, *et al*. Entecavir combined with Fufang Biejia Ruangan tablet in treatment of chronic hepatitis B patients with liver fibrosis: 96-week efficacy analyses. Nan Fang Yi Ke Da Xue Xue Bao 2016;36(6):775–779. Chinese. doi:10.3969/j.issn.1673-4254.2016.06.07, PMID:27320877.
[39] Xiao HM, Shi MJ, Jiang JM, Cai GS, Xie YB, Tian GJ, *et al*. Efficacy and safety of AnluoHuaxian pills on chronic hepatitis B with normal or minimally elevated alanine transaminase and early liver fibrosis: A randomized controlled trial. J Ethnopharmacol 2022;293:115210. doi:10.1016/j.jep.2022.115210, PMID:35398501.
[40] Wang Z, Xie YW, Lu Q, Yan HL, Liu XB, Long Y, *et al*. The impact of albumin infusion on the risk of rebleeding and in-hospital mortality in cirrhotic patients admitted for acute gastrointestinal bleeding: a retrospective study of a single institute. BMC Gastroenterol 2020;20(1):198. doi:10.1186/s12876-020-01337-5, PMID:32576140.
[41] Fernández J, Clària J, Amorós A, Aguilar F, Castro M, Casulleras M, *et al*. Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic Inflammation in Patients With Decompensated Cirrhosis. Gastroenterology 2019;157(1):149–162. doi:10.1053/j.gastro.2019.03.021, PMID:30905652.
[42] Qi XS, Bao YX, Bai M, Xu WD, Dai JN, Guo XZ. Nonselective beta-blockers in cirrhotic patients with no or small varices: A meta-analysis. World J Gastroenterol 2015;21(10):3100–3108. doi:10.3748/wjg.v21.i10.3100, PMID:25780311.
[43] Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, *et al*. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62(11):1634–1641. doi:10.1136/gutjnl-2012-304038, PMID:23250049.
[44] Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database Syst Rev 2012;(8):CD004544. doi:10.1002/14651858.CD004544.pub2, PMID:22895942.
[45] Hernández-Gea V, Aracil C, Colomo A, Garupera I, Poca M, Torras X, *et al*. Development of ascites in compensated cirrhosis with severe portal hypertension treated with β-blockers. Am J Gastroenterol 2012;107(3):418–427. doi:10.1038/ajg.2011.456, PMID:22334252.
[46] Pose E, Trebicka J, Mookerjee RP, Angeli P, Ginès P. Statins: Old drugs as new therapy for liver diseases? J Hepatol 2019;70(1):194–202. doi:10.1016/j.jhep.2018.07.019, PMID:30075229.
[47] Gluud LL, Langholz E, Krag A. Meta-analysis: isosorbide-mononitrate alone or with either beta-blockers or endoscopic therapy for the management of oesophageal varices. Aliment Pharmacol Ther 2010;32(7):859–871. doi:10.1111/j.1365-2036.2010.04418.x, PMID:20839387.
[48] Herath CB, Grace JA, Angus PW. Therapeutic potential of targeting the renin angiotensin system in portal hypertension. World J Gastrointest Pathophysiol 2013;4(1):1–11. doi:10.4291/wjgp.v4.i1.1, PMID:23596549.
[49] Kim DH, Park JY. Prevention and management of variceal hemorrhage. Int J Hepatol 2013;2013:434609. doi:10.1155/2013/434609, PMID:23606973.
[50] Karadsheh Z, Allison H. Primary prevention of variceal bleeding: pharmacological therapy versus endoscopic banding. N Am J Med Sci 2013;5(10):573–579. doi:10.4103/1947-2714.120791, PMID:24350068.
[51] de Mattos ÂZ, Terra C, Farias AQ, Bittencourt PL, Alliance of Brazilian Centers for Cirrhosis Care–the ABC Group. Primary prophylaxis of variceal bleeding in patients with cirrhosis: A comparison of different strategies. World J Gastrointest Endosc 2021;13(12):628–637. doi:10.4253/wjge.v13.i12.628, PMID:35070024.
[52] Bai M, Qi X, Yang M, Han G, Fan D. Combined therapies versus monotherapies for the first variceal bleeding in patients with high-risk varices: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2014;29(3):442–452. doi:10.1111/jgh.12396, PMID:24118091.
[53] Mishra SR, Sharma BC, Kumar A, Sarin SK. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. J Hepatol 2011;54(6):1161–1167. doi:10.1016/j.jhep.2010.09.031, PMID:21145834.
[54] Chinese Society of Hepatology, Chinese Medical Association. Consensus on secondary prevention of primary liver cancer (2021 version). Zhonghua Gan Zang Bing Za Zhi 2021;29(3):216–226. Chinese. doi:10.3760/cma.j.cn501113-20210210-00082, PMID:33902188.
[55] O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology 2019;157(1):34–43.e1. doi:10.1053/j.gastro.2019.03.070, PMID:30986390.
[56] Drebes A, de Vos M, Gill S, Fosbury E, Mallett S, Burroughs A, *et al*. Prothrombin Complex Concentrates for Coagulopathy in Liver Disease: Single-Center, Clinical Experience in 105 Patients. Hepatol Commun 2019;3(4):513–524. doi:10.1002/hep4.1293, PMID:30976742.
[57] Gralnek IM, Stanley AJ, Morris AJ, Camus M, Lau J, Lanas A, *et al*. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021. Endoscopy 2021;53(3):300–332. doi:10.1055/a-1369-5274, PMID:33567467.
[58] Lau JYW, Yu Y, Tang RSY, Chan HCH, Yip H-C, Chan SM, *et al*. Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding. N Engl J Med 2020;382(14):1299–1308. doi:10.1056/NEJMoa1912484, PMID:32242355.
[59] Jung DH, Huh CW, Kim NJ, Kim B-W. Optimal endoscopy timing in patients with acute variceal bleeding: A systematic review and meta-analysis. Sci Rep 2020;10(1):4046. doi:10.1038/s41598-020-60866-x, PMID:32132589.
[60] Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, *et al*. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology (Baltimore, Md) 2014;60(3):954–963. doi:10.1002/hep.27006, PMID:24415445.
[61] Zhou X, Tripathi D, Song T, Shao L, Han B, Zhu J, *et al*. Terlipressin for the treatment of acute variceal bleeding: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97(48):e13437. doi:10.1097/MD.0000000000013437, PMID:30508958.
[62] Jha SK, Mishra M, Jha A, Dayal VM. Comparison of continuous versus intermittent infusions of terlipressin for the control of acute variceal bleeding in patients with portal hypertension: An open-label randomized controlled trial. Indian J Gastroenterol 2018;37(4):313–320. doi:10.1007/s12664-018-0871-8, PMID:30132224.
[63] Triantos C, Kalafateli M, Assimakopoulos SF, Karaivazoglou K, Mantaka A, Aggeletopoulou I, *et al*. Endotoxin Translocation and Gut Barrier Dysfunction Are Related to Variceal Bleeding in Patients With Liver Cirrhosis. Front Med (Lausanne) 2022;9:836306. doi:10.3389/fmed.2022.836306, PMID:35308545.
[64] Martínez J, Hernández-Gea V, Rodríguez-de-Santiago E, Téllez L, Procopet B, Giráldez Á, *et al*. Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis. J Hepatol 2021;75(2):342–350. doi:10.1016/j.jhep.2021.03.026, PMID:33845059.
[65] Lin L, Cui B, Deng Y, Jiang X, Liu W, Sun C. The Efficacy of Proton Pump Inhibitor in Cirrhotics with Variceal Bleeding: A Systemic Review and Meta-Analysis. Digestion 2021;102(2):117–127. doi:10.1159/000505059, PMID:32088712.
[66] Janka T, Tornai T, Borbély B, Tornai D, Altorjay I, Papp M, *et al*. Deleterious effect of proton pump inhibitors on the disease course of cirrhosis. Eur J Gastroenterol Hepatol 2020;32(2):257–264. doi:10.1097/MEG.0000000000001499, PMID:31464790.
[67] An Y, Bai Z, Xu X, Guo X, Romeiro FG, Philips CA, *et al*. No Benefit of Hemostatic Drugs on Acute Upper Gastrointestinal Bleeding in Cirrhosis. Biomed Res Int 2020;2020:4097170. doi:10.1155/2020/4097170, PMID:32685481.
[68] Bates D, Edwards J, Langevin A, Abu-Ulba A, Yallou F, Wilson B, *et al*. Rebleeding in Variceal and Nonvariceal Gastrointestinal Bleeds in Cirrhotic Patients Using Vitamin K: The LIVER-K Study. Can J Hosp Pharm 2020;73(1):19–26. PMID:32109957.
[69] Anand AC. Nutrition and Muscle in Cirrhosis. J Clin Exp Hepatol 2017;7(4):340–357. doi:10.1016/j.jceh.2017.11.001, PMID:29234200.
[70] Wang R, Huang X, Zhou T, Li Y, Ding M, Xu H, *et al*. Safety and feasibility of early oral nutrition after endoscopic treatment for patients with liver cirrhosis: A historical prospective and comparative effectiveness study. JPEN J Parenter Enteral Nutr 2022;46:1660–1670. doi:10.1002/jpen.2328, PMID:35040175.
[71] Lo G-H, Lin C-W, Hsu Y-C. A controlled trial of early versus delayed feeding following ligation in the control of acute esophageal variceal bleeding. J Chin Med Assoc 2015;78(11):642–647. doi:10.1016/j.jcma.2015.07.004, PMID:26341455.
[72] Huang Y, Zhang W, Xiang H, Liu Y, Yuan L, Zhang L, *et al*. Treatment Strategies in Emergency Endoscopy for Acute Esophageal Variceal Bleeding (CHESS1905): A Nationwide Cohort Study. Front Med (Lausanne) 2022;9:872881. doi:10.3389/fmed.2022.872881, PMID:35572990.
[73] Goral V, Yılmaz N. Current Approaches to the Treatment of Gastric Varices: Glue, Coil Application, TIPS, and BRTO. Medicina (Kaunas) 2019;55(7):335. doi:10.3390/medicina55070335, PMID:31277322.
[74] Hu Z, Zhang D, Swai J, Liu T, Liu S. Risk of rebleeding from gastroesophageal varices after initial treatment with cyanoacrylate; a systematic review and pooled analysis. BMC Gastroenterol 2020;20(1):181. doi:10.1186/s12876-020-01333-9, PMID:32517718.
[75] Gillespie S-L, McAvoy NC, Yung DE, Robertson A, Plevris JN, Hayes PC. Thrombin Is an Effective and Safe Therapy in the Management of Bleeding Gastric Varices. A Real-World Experience. J Clin Med 2021;10(4):785. doi:10.3390/jcm10040785, PMID:33669257.
[76] Mohan BP, Chandan S, Khan SR, Kassab LL, Trakroo S, Ponnada S, *et al*. Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis. Endoscopy 2020;52(4):259–267. doi:10.1055/a-1098-1817, PMID:32028533.
[77] Li B, Chen J, Zhang C-Q, Wang G-C, Hu J-H, Luo J-J, *et al*. The pharmacodynamic effect of terlipressin versus high-dose octreotide in reducing hepatic venous pressure gradient: a randomized controlled trial. Ann Transl Med 2021;9(9):793. doi:10.21037/atm-20-6774, PMID:34268406.
[78] Lau LHS, Sung JJY. Treatment of upper gastrointestinal bleeding in 2020: New techniques and outcomes. Dig Endosc 2021;33(1):83–94. doi:10.1111/den.13674, PMID:32216134.
[79] Bridwell RE, Long B, Ramzy M, Gottlieb M. Balloon Tamponade for the Management of Gastrointestinal Bleeding. J Emerg Med 2022;62(4):545–558. doi:10.1016/j.jemermed.2021.11.004, PMID:35065859.
[80] Lv Y, Yang Z, Liu L, Li K, He C, Wang Z, *et al*. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients

with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4(8):587–598. doi:10.1016/S2468-1253(19)30090-1, PMID:31153882.
[81] Kumar R, Kerbert AJC, Sheikh MF, Roth N, Calvao JAF, Mesquita MD, *et al*. Determinants of mortality in patients with cirrhosis and uncontrolled variceal bleeding. J Hepatol 2021;74(1):66–79. doi:10.1016/j.jhep.2020.06.010, PMID:32561318.
[82] Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, Garcia E, *et al*. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol 2020;73(5):1082–1091. doi:10.1016/j.jhep.2020.04.024, PMID:32339602.
[83] Wang ZW, Liu JC, Zhao F, Zhang WG, Duan XH, Chen PF, *et al*. Comparison of the Effects of TIPS versus BRTO on Bleeding Gastric Varices: A Meta-Analysis. Can J Gastroenterol Hepatol 2020;2020:5143013. doi:10.1155/2020/5143013, PMID:32104670.
[84] Luo X, Xiang T, Wu J, Wang X, Zhu Y, Xi X, *et al*. Endoscopic Cyanoacrylate Injection Versus Balloon-Occluded Retrograde Transvenous Obliteration for Prevention of Gastric Variceal Bleeding: A Randomized Controlled Trial. Hepatology (Baltimore, Md) 2021;74(4):2074–2084. doi:10.1002/hep.31718, PMID:33445218.
[85] Chinese Society of Spleen and Portal Hypertension Surgery, Chinese Medicine Association. Expert consensus on diagnosis and treatment of esophagogastric variceal bleeding in cirrhotic portal hypertension(2019 edition). Zhonghua Wai Ke Za Zhi 2019;18(12):1087–1093. Chinese. doi:10.3760/cma.j.issn.1673-9752.2019.12.001, PMID:31826590.
[86] Magaz M, Baiges A, Hernández-Gea V. Precision medicine in variceal bleeding: Are we there yet? J Hepatol 2020;72(4):774–784. doi:10.1016/j.jhep.2020.01.008, PMID:31981725.
[87] Sheng J-Y, Liu S, Yang Y-S, Zhang X-W. The prognosis in management of esophagogastric bleeding in cirrhotic portal hypertension. Zhonghua Wai Ke Za Zhi 2020;58(10):808–812. Chinese. doi:10.3760/cma.j.cn112139-20191111-00556, PMID:32993269.
[88] Plaz Torres MC, Best LM, Freeman SC, Roberts D, Cooper NJ, Sutton AJ, *et al*. Secondary prevention of variceal bleeding in adults with previous oesophageal variceal bleeding due to decompensated liver cirrhosis: a network meta-analysis. Cochrane Database Syst Rev 2021;3:CD013122. doi:10.1002/14651858.CD013122.pub2, PMID:33784794.
[89] Tian S, Li R, Guo Y, Jia X, Dong W. Carvedilol vs endoscopic band ligation for the prevention of variceal bleeding: a meta-analysis. Ther Clin Risk Manag 2019;15:191–200. doi:10.2147/TCRM.S193196, PMID:30774355.
[90] Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database Syst Rev 2018;10:CD011510. doi:10.1002/14651858.CD011510.pub2, PMID:30372514.
[91] Baiges A, Hernández-Gea V, Bosch J. Pharmacologic prevention of variceal bleeding and rebleeding. Hepatol Int 2018;12(Suppl 1):68–80. doi:10.1007/s12072-017-9833-y, PMID:29210030.
[92] Rajapaksha IG, Gunarathne LS, Angus PW, Herath CB. Update on New Aspects of the Renin-Angiotensin System in Hepatic Fibrosis and Portal Hypertension: Implications for Novel Therapeutic Options. J Clin Med 2021;10(4):702. doi:10.3390/jcm10040702, PMID:33670126.
[93] Shi L, Zhang X, Li J, Bai X. Favorable Effects of Endoscopic Ligation Combined with Drugs on Rebleeding and Mortality in Cirrhotic Patients: A Network Meta-Analysis. Dig Dis 2018;36(2):136–149. doi:10.1159/000484082, PMID:29161702.
[94] Yan Y, Li Y, Fan C, Zhang Y, Zhang S, Wang Z, *et al*. A novel machine learning-based radiomic model for diagnosing high bleeding risk esophageal varices in cirrhotic patients. Hepatol Int 2022;16(2):423–432. doi:10.1007/s12072-021-10292-6, PMID:35366193.
[95] Paternostro R, Becker J, Hofer BS, Panagl V, Schiffke H, Simbrunner B, *et al*. The prognostic value of HVPG-response to non-selective beta-blockers in patients with NASH cirrhosis and varices. Dig Liver Dis 2022;54(4):500–508. doi:10.1016/j.dld.2021.09.009, PMID:34799282.
[96] Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, *et al*. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393(10181):1597–1608. doi:10.1016/S0140-6736(18)31875-0, PMID:30910320.
[97] Zheng J, Zhang Y, Li P, Zhang S, Li Y, Li L, *et al*. The endoscopic ultrasound probe findings in prediction of esophageal variceal recurrence after endoscopic variceal eradication therapies in cirrhotic patients: a cohort prospective study. BMC Gastroenterol 2019;19(1):32. doi:10.1186/s12876-019-0943-y, PMID:30782139.
[98] Dai C, Liu W-X, Jiang M, Sun M-J. Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: a meta-analysis. World J Gastroenterol 2015;21(8):2534–2541. doi:10.3748/wjg.v21.i8.2534, PMID:25741164.
[99] Dunne PDJ, Young D, Chuah CS, Hayes PC, Tripathi D, Leithead J, *et al*. Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding-Long-term follow-up of a randomised control trial. Aliment Pharmacol Ther 2022;55(12):1581–1587. doi:10.1111/apt.16901, PMID:35322892.
[100] Miao Z, Lu J, Yan J, Lu L, Ye B, Gu M. Comparison of Therapies for Secondary Prophylaxis of Esophageal Variceal Bleeding in Cirrhosis: A Network Meta-analysis of Randomized Controlled Trials. Clin Ther 2020;42(7):1246–1275.e3. doi:10.1016/j.clinthera.2020.04.014, PMID:32624321.
[101] Osman KT, Nayfeh T, Abdelfattah AM, Alabdallah K, Hasan B, Firwana M, *et al*. Secondary Prophylaxis of Gastric Variceal Bleeding: A Systematic Review and Network Meta-Analysis. Liver Transpl 2022;28(6):945–958. doi:10.1002/lt.26383, PMID:34860458.
[102] Yoo J-J, Kim SG, Kim YS, Lee B, Jeong SW, Jang JY, *et al*. Propranolol plus endoscopic ligation for variceal bleeding in patients with significant ascites: Propensity score matching analysis. Medicine (Baltimore) 2020;99(5):e18913. doi:10.1097/MD.0000000000018913, PMID:32000397.
[103] Alvi H, Zuberi BF, Rasheed T, Ibrahim MA. Evaluation of endoscopic variceal band ligation sessions in obliteration of esophageal varices. Pak J Med Sci 2020;36(2):37–41. doi:10.12669/pjms.36.2.1144, PMID:32063928.
[104] House T, Webb P, Baarson C. Massive Hemorrhage from Ectopic Duodenal Varices: Importance of a Multidisciplinary Approach. Case Rep Gastroenterol 2017;11(1):36–41. doi:10.1159/000455184, PMID:28203136.
[105] Zhan C, Prabhu V, Kang SK, Li C, Zhu Y, Kim S, *et al*. Comparison of Non-Tumoral Portal Vein Thrombosis Management in Cirrhotic Patients: TIPS Versus Anticoagulation Versus No Treatment. J Clin Med 2021;10(11):2316. doi:10.3390/jcm10112316, PMID:34073236.
[106] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022;76(5):1151–1184. doi:10.1016/j.jhep.2021.09.003, PMID:35300861.
[107] Luo J, Li M, Wu C, Zhu D, Wang H, Huang M, *et al*. Transjugular intrahepatic portosystemic shunt versus endoscopic therapy for prevention of variceal rebleeding in patients with hepatocellular carcinoma meeting the Milan criteria. Eur J Gastroenterol Hepatol 2021;33(3):436–442. doi:10.1097/MEG.0000000000001750, PMID:32398493.