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Review paper

Surveillance for portal hypertension in the course of liver cirrhosis

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Abstract

Non-invasive liver fibrosis assessment techniques are under development for evaluating the severity of liver disease and portal hypertension. The paper presents practical arrangements for the diagnosis and treatment of portal hypertension in patients with chronic liver disease, established in the Baveno VI Consensus Workshop for diagnosis and treatment of portal hypertension. Currently, the diagnostic standard of liver disease severity is transient elastography, which can identify patients with clinically significant portal hypertension (liver stiffness > 20 kPa). The paper presents the eligibility criteria for endoscopy and the principle of repeating the assessment of oesophageal varices. It also describes the primary and secondary prevention of gastroesophageal haemorrhage, the treatment of oesophageal bleeding and the treatment of liver vessel thrombosis.

Key words: portal hypertension, liver cirrhosis, transient elastography, endoscopy, oesophageal varices, gastrointestinal bleeding.

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Introduction

In recent years, new non-invasive techniques have been developed for staging hepatic fibrosis and assessing the severity of portal hypertension in liver cirrhosis.

Since 1990, regular international conferences held in Baveno, Italy have evaluated the practical arrangements for diagnosis of portal hypertension in patients with chronic liver disease. The most recent edition of the Baveno recommendations, published in 2015 following the Baveno VI Consensus Workshop, describes non-invasive methods for the assessment of liver fibrosis in patients with portal hypertension [1].

Pathogenesis of portal hypertension

Portal hypertension occurs as a consequence of haemodynamic alterations in the course of liver cirrhosis, and is responsible for severe complications such as ascites, hepatic encephalopathy and variceal bleeding. The term refers to a pathological increase in portal pressure associated with vascular resistance to the portal blood flow caused by architectural modifications of the liver. The increased vascular resistance to portal blood flow results from the active contraction of portal blood vessels, caused by simultaneous accumulation of collagen tissue in the liver and decreased intrahepatic endothelial synthesis of nitric oxide. This phenomenon also affects the splanchnic arteriolar and systemic circulation by the vasodilation of arterioles in the splanchnic organs and collateral vessel formation, contributing to increased portal venous flow and the exacerbation of portal hypertension. In contrast to liver endothelial cells, the increased production of nitric oxide by hyperactive splanchnic endothelial cells alleviates portal hypertension [2] (Fig. 1).

Diagnosis of portal hypertension

Clinically significant portal hypertension (CSPH) is reported in some patients with compensated liver cirrhosis, or compensated advanced chronic liver disease (cACLD).

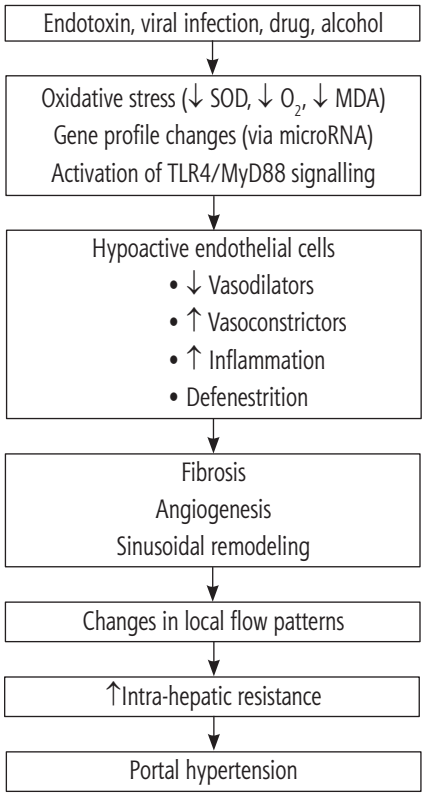


Fig. 1. Pathogenesis of portal hypertension according to [2]

The Baveno VI guidelines propose that liver stiffness measurement by transient elastography is sufficient to suspect cACLD in asymptomatic patients with established chronic liver disease.

However, transient elastography (TE) often provides false positive results; hence two measurements of liver stiffness on different days under fasting conditions are recommended.

In asymptomatic patients, liver stiffness values < 10 kPa exclude cACLD, values between 10 and 15 kPa are suggestive of cACLD but further testing is needed to confirm it, while values > 15 kPa are accurate enough to identify patients with cACLD.

The diagnosis of compensated liver cirrhosis is based on invasive methods as follows:
– liver biopsy assessing staging of liver fibrosis and liver cirrhosis,
– measurement of collagen proportionate area (CPA) in the liver tissue obtained by liver biopsy,
– endoscopy revealing the presence of gastroesophageal varices,
– measurement of the hepatic venous pressure gradient (HVPG); HVPG values above 5 mmHg suggest portal hypertension.

Substantial portal hypertension is defined as HVPG ≥ 10 mmHg. This HVPG value has some clinical implications, as patients with a HVPG < 10 mmHg have a very low risk of varices and do not require screening endoscopy [3].

When should screening endoscopy be performed in patients with portal hypertension?

In patients with viral chronic liver diseases, non-invasive methods are sufficient to exclude clinically significant portal hypertension.

Patients with liver stiffness indicated by a transient elastography value < 20 kPa and platelet counts over 150,000 mm^{-3} have a lower risk of developing oesophageal varices, and no screening gastroscopy or treatment is necessary. However, the assessment of liver stiffness and platelet count should be repeated every year, and gastroscopy is recommended in cases of progression indicated by changes in transient elastography score and decreased platelet count.

Validation of Baveno VI criteria was performed by Maurice *et al*. in 2016 in a study that included 310 patients and the authors concluded that the criteria correctly identify 98% of patients who could safely avoid endoscopy [4].

Jangouk *et al*. evaluated retrospectively patients with liver stiffness > 10 kPa who had liver stiffness and endoscopy within 1 year of each other. In this study that included 161 patients, the authors found that the sensitivity and negative predictive value of Baveno VI criteria were 100% [5]. Another analysis verified the Baveno VI criteria as identifying compensated cirrhotic patients without varices requiring treatment in whom screening endoscopy could have been avoided safely [6].

On the other hand, Mattos and Mattos discussed the methodology of some studies used as a basis of the Baveno VI Consensus and concluded that non-invasive methods "should not replace endoscopy in variceal screening at the present time" [7].

In EASL-ALEH Clinical Practice Guidelines of non-invasive tests used for evaluating liver fibrosis and disease progression, the authors concluded that there is increasing evidence for the prognostic value of non-invasive tests, particularly LS measurement using TE, in patients with cirrhosis, but non-invasive tests cannot replace HVPG for a detailed PH evaluation and upper GI endoscopy for detecting varices [8].

AASLD Recommendations from 2017 incorporated Baveno VI criteria and concluded that patients with an LS < 20 kPa and platelet count > 150,000/mm^3 have a very low probability (< 5%) of having high-risk varices, and oesophagogastroduodenoscopy can be circumvented. In patients who do not meet these criteria,

screening endoscopy for the diagnosis of gastroesophageal varices is recommended when the diagnosis of cirrhosis is made [9].

How often should endoscopy be repeated in patients with portal hypertension?

Patients with ongoing chronic liver disease (e.g. active drinking in alcoholics, lack of sustained virological response [SVR] in HCV) with no varices on initial endoscopy should undergo endoscopic screening for varices every two years. In those who have small varices, surveillance endoscopy should be repeated every one to two years. In compensated patients without co-factors (e.g. obesity), but with small varices identified by the initial endoscopy, and in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics), surveillance endoscopy is necessitated at two-year intervals [1] (Fig. 2).

The influence of etiological therapy on portal hypertension in patients with liver cirrhosis

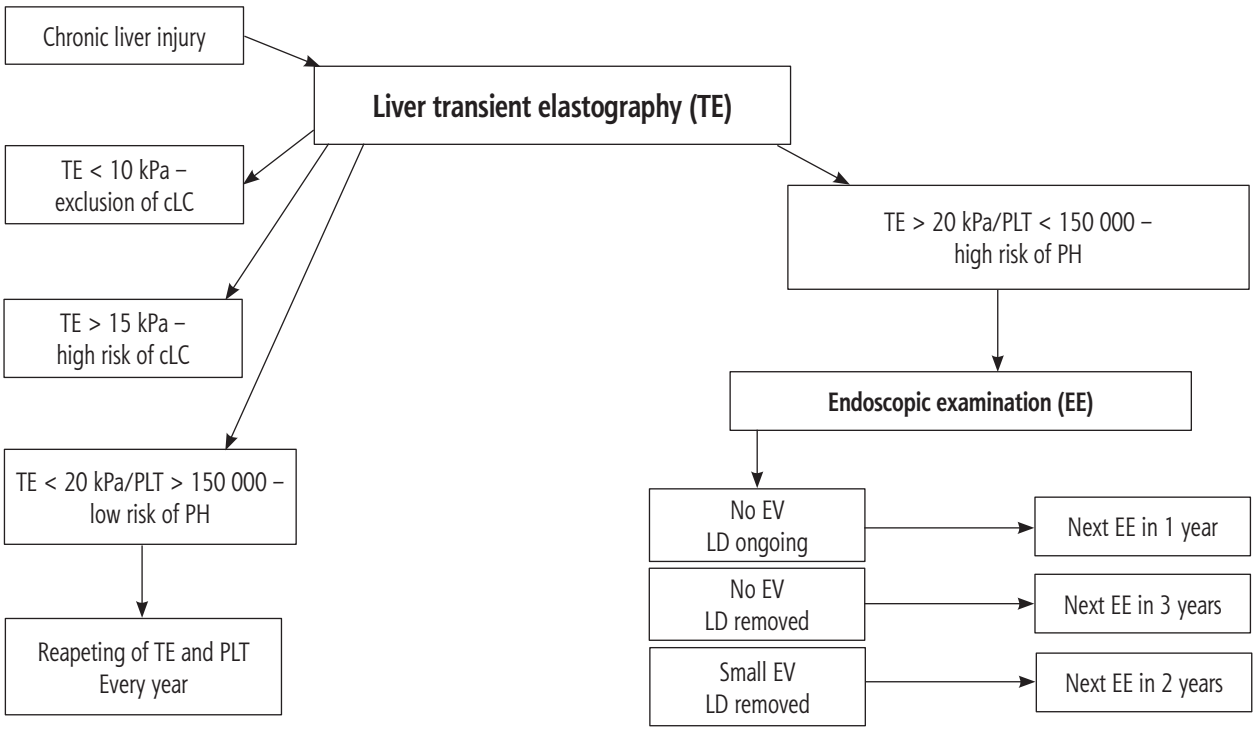
The successful treatment of the underlying disease improves the architecture and function of the liver, leading to a reduction in portal hypertension and preventing variceal bleeding – a complication of liver cirrhosis [10-12]. The measurement of HVPG is an acceptable predictor of clinical outcome in patients with non-cholestatic cirrhosis, with a change in HVPG of 10% or more being considered significant. On the other hand, alcohol consumption and obesity may influence the course of portal hypertension after successful aetiological therapy [1, 13].

Management in patients with small varices

Patients with small varices do not require beta blockers to prevent the formation of varices. However, treatment with non-selective beta blockers (NSBB) is recommended in patients with small varices with red wale marks or those of Child-Pugh class C, who are at higher risk of variceal bleeding [1, 14].

Management in patients with medium-large varices

In patients with medium or large varices, either NSBB or endoscopic band ligation is recommended for the prevention of initial variceal bleeding [1, 15]. The choice of an appropriate treatment should be



EV – esophageal varices, LD – liver disease

Fig. 2. Algorithm of management in patients with compensated liver cirhosis (cLC), liver cirrhosis (LC) and portal hypertension (PH), according to the Consensus Baveno VI

based on local knowledge and experience, patient preferences, existing contraindications and adverse events. Among traditional NSBB, propranolol, nadolol and carvedilol are first-line treatments.

Management in patients with gastric varices

Cyanoacrylate injection is recommended in patients with large gastroesophageal varices or isolated gastric varices. This approach is more effective than beta blockers in preventing the first bleeding from gastroesophageal or gastric varices. However, available data are limited and based on the results of only a few studies. Treatment with NSBB should be closely monitored in patients with liver disease progression, even in those without prior existing contraindications to NSBB therapy.

NSBB drugs should be used with caution, and the dosage should be individually adjusted in patients with end-stage disease (refractory ascites and/or spontaneous bacterial peritonitis). It is necessary to monitor the blood pressure in these patients, because there is a high risk of impaired renal function. If the NSBB therapy is discontinued, the patient will need oesophageal band ligation.

HVPG measurement is an invasive method and is not routinely used in clinical practice to assess the indication for NS5B and the response to this treatment.

HVPG measurement is the most accurate method of monitoring portal hypertension. A decrease in HVPG of 10% from baseline or to 12 mmHg indicates that NSBB therapy was successful in the primary prevention of variceal bleeding [1, 16, 17].

Management of acute oesophageal variceal bleeding

Conservative treatment:
- blood volume restitution to preserve tissue perfusion,
- red blood cell transfusion should be performed conservatively at a target haemoglobin level between 7 and 8 g/dl,
- ceftriaxone is used as antibiotic prophylaxis by intravenous infusion at a rate of 1 g/24 hours,
- prevention of hepatic encephalopathy using lactulose or rifaximin, lactulose at a dose of 25 ml/12 hours until two or three soft bowel movements are produced, followed by dose titration to maintain two or three soft bowel movements per day,
- the use of vasoactive drugs (terlipressin, somatostatin, octreotide) is recommended as soon as possible before endoscopic therapy and continued for up to five days.

Invasive treatment:
- oesophagogastroduodenoscopy within 12 hours of bleeding,
- pre-endoscopic infusion of erythromycin (250 mg *i.v.* 30-120 min before endoscopy) in the absence of QT prolongation,
- ligation is the preferred method of endoscopic therapy for acute oesophageal variceal bleeding; however, endoscopic therapy with a tissue adhesive (e.g. N-butylcyanoacrylate) is recommended for patients with acute bleeding from isolated gastric varices (IGV) and those with type 2 gastroesophageal varices that extend beyond the cardia,
- early implantation of TIPS (transjugular intrahepatic portosystemic shunt) with PTFE (polytetrafluoroethylene)-covered stents within 72 hours (ideally < 24 hours) in patients at high risk of treatment failure (e.g. Child-Pugh class C < 14 points or Child-Pugh class B with active bleeding); TIPS is the best option in cases of rebleeding (during the first five days after the first bleeding),
- a balloon tamponade should only be used in refractory oesophageal bleeding as a temporary "bridge" (for a maximum of 24 hours) until definitive treatment can be instituted: self-expanding oesophageal metal stents are a more efficacious and safer option for these patients than a balloon tamponade.

No recommendations exist for the management of coagulopathy including thrombocytopenia in patients with variceal bleeding [1, 18].

Prevention of recurrent variceal haemorrhage

The combination of NSBB (propranolol or nadolol) and endoscopic variceal ligation (EVL) is recommended to prevent recurrent variceal haemorrhage. Carvedilol cannot be used in the prevention of rebleeding as no existing studies compare carvedilol to the current standard of care. If there are contraindications to NSBB, EVL should not be used as monotherapy.

Pharmacological monotherapy can be used only in patients who are unable to be treated with EVL.

In cases of combined treatment failure (NSBB and EVL), the placement of covered TIPS should be undertaken as a rescue therapy for the prevention of recurrent variceal haemorrhage [1, 19].

Secondary prophylaxis of recurrent variceal haemorrhage in patients with end-stage liver disease, for instance in patients with refractory ascites, has some limitations. In patients with advanced portal hypertension, NSBB should be used cautiously with close monitoring of clinical and laboratory parameters. Treat-

ment with NSBB should be reduced or discontinued in the following cases:
– systolic blood pressure < 90 mmHg,
– hyponatraemia (< 13 mEq/l),
– acute kidney injury [1, 20, 21].

Management in vascular diseases of the liver leading to portal hypertension in cirrhotic and non-cirrhotic patients

Primary thrombosis of the portal or hepatic venous system

Primary thrombosis of the portal vein (PVT) or hepatic venous system is associated with hyperactivity of prothrombotic factors occurring in the course of inherited or acquired coagulopathy, as well as paroxysmal nocturnal haemoglobinuria and autoimmune disorders. Nowadays, low molecular weight heparin and vitamin K antagonists are recommended in the treatment of thrombosis of the portal venous system. Further clinical trials are required to assess the safety and efficacy of these direct oral anticoagulants and antiplatelet drugs. Currently, available treatment guidelines propose routine screening for PVT in all patients on the waiting list for a liver transplant; Doppler ultrasonography should be performed every six months in these patients. A diagnosis of thrombosis of the main portal vein trunk, or progressive PVT, in potential candidates for liver transplantation is an indication for anticoagulation therapy.

However, in untreated patients, follow-up examination by colour Doppler imaging is recommended every three months and anticoagulation therapy can be instituted in cases of thrombosis progression; however, anticoagulation treatment is not recommended in non-candidates for liver transplantation, except for cases of thrombosis in the superior mesenteric vein.

Anticoagulation treatment could also lead to complications in patients with low platelet counts and PVT due to the higher risk of gastrointestinal bleeding. In such cases, the decision to use the treatment should be considered on an individual basis.

Extrahepatic portal vein obstruction (EHPVO)

EHPVO can occur with or without involvement of the intrahepatic portal veins, although this definition does not include isolated thrombosis of the splenic vein or the superior mesenteric vein. EHPVO is characterized by features of recent thrombosis or portal hypertension, with portal cavernoma as a sequel of portal vein obstruction. In cases of EHPVO, liver cirrhosis and malignancies definitely should be excluded.

Doppler ultrasonography, and CT or MRI angiography can reveal obstruction of the portal vein, or the presence of solid intraluminal material or portal vein cavernoma in cases of EHPVO. Liver biopsy and HVPG can be considered only in cases of dysmorphism revealed by liver imaging or abnormal liver tests. Low molecular weight heparin should be initiated immediately followed by oral anticoagulant therapy. Anticoagulation should be used for at least six months. Although the duration of the maintenance therapy has not been precisely established, long-term anticoagulation is preferred. It is essential to introduce anticoagulation treatment after starting prophylaxis of variceal haemorrhage. In cases of concomitant infection, antibiotic therapy is needed. Early introduction of anticoagulant treatment is needed to enable full recanalization of the portal vein. In patients with persistent abdominal pain, bloody diarrhoea and lactic acidosis, surgical intervention should be considered. Failure of recanalization and persistent thrombosis are indications for diagnostic gastroscopy within six months of the acute episode. In the absence of varices, endoscopy should be repeated after one and two years.

Unfortunately, insufficient data exist on the use of beta blockers or endoscopic therapy as the preferred option in primary prophylaxis of variceal haemorrhage in the course of EHPVO. However, the evidence indicates that the above-mentioned methods are equally effective for secondary prophylaxis of variceal haemorrhage. The implementation of mesenteric-left portal vein bypass (Meso-Rex operation) should be considered in all children with complications of chronic EHPVO. The measurement of HVPG is the preferred diagnostic tool in chronic EHPVO.

Idiopathic portal hypertension (IPH)

IPH is a rare disease reported in the course of autoimmune disorders and prothrombotic conditions (e.g. thrombophilia). In every such case, liver cirrhosis should be excluded. Liver biopsy and HVPG measurement are used for diagnosis. Doppler ultrasonography should be performed at least every six months to identify the development of PVT and to indicate anticoagulation therapy.

Budd-Chiari syndrome/hepatic venous outflow tract obstruction (BCS/HVOTO)

BCS/HVOTO is the impairment of hepatic venous outflow in the small hepatic veins, the inferior vena

cava or right atrium of the heart. The primary cause of thrombosis in Budd-Chiari syndrome is unknown. Secondary Budd-Chiari syndrome is associated with compression of the hepatic venous system by tumours, liver cancer infiltration, abscesses or cysts. Intraluminal material can be observed in the hepatic veins and portosystemic collaterals under Doppler imaging. Although liver biopsy is not routinely recommended in such cases, it may reveal thromboses in small hepatic veins. Hepatocellular carcinoma surveillance is advisable for patients with BCS/HVOTO. The therapeutic options for BCS/HVOTO include anticoagulation therapy, angioplasty with thrombolytic therapy, TIPS placement or liver transplantation. Pharmacological therapy and endoscopic surveillance in patients with BCS/HVOTO are the same as the management in EHPVO [1].

Disclosure

Authors report no conflict of interest.

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