Techniques in Gastrointestinal Endoscopy 19 (2017) 84–89

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Primary and secondary prophylaxis of esophageal variceal bleeding

Parastoo Jangouk, MD[a,b], Guadalupe Garcia-Tsao, MD[a,b,*]

[a] Section of Digestive Diseases, Department of Medicine, Veterans Administration Connecticut Healthcare System, West Haven, Connecticut
[b] Section of Digestive Diseases, Department of Medicine, Yale University, New Haven, Connecticut

ARTICLE INFO

Article history:
Received 23 January 2017
Accepted 23 March 2017

Keywords:
Portal hypertension
Variceal hemorrhage
Cirrhosis
Esophageal varices
Primary prophylaxis
Secondary prophylaxis

ABSTRACT

Cirrhosis is a chronic condition with high-mortality. Portal hypertension (PH) is the initial and main consequence of cirrhosis and is responsible for most of its complications, including esophageal varices. A portal pressure, as determined by the hepatic venous pressure gradient (HVPG) $>$ 5 mm Hg defines PH. When the HVPG reaches 10 mm Hg or greater, the patient with compensated cirrhosis has developed clinically significant PH and is at a higher risk of developing varices and clinical decompensation. Patients with varices that have not bled are still in the compensated stage but are at a higher risk of decompensation than those without varices. Variceal hemorrhage constitutes a decompensating event, but its mortality differs whether it presents as an isolated complication of cirrhosis (20% 5-year mortality) or whether it presents in association with other complications (more than 80% 5-year mortality). While in the past, emphasis had been placed on managing the direct complications of PH, varices and variceal hemorrhage, it is now clear that these complications cannot be considered in an isolated manner. Rather, they should be considered in the context of advances in the staging of cirrhosis and other complications of cirrhosis that might occur concomitant or subsequent to the development of varices and variceal hemorrhage.

1. Introduction

Portal hypertension (PH) plays a major role in the development of the most severe complications of cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastroesophageal varices. Variceal formation and variceal hemorrhage are complications of cirrhosis that result most directly from PH. As in any other venous system, portal pressure is expressed as a gradient, in this case between the portal vein and the inferior vena cava. The most common method of assessing the portosystemic gradient is by catheterizing the hepatic vein and measuring the wedged pressure (portal sinusoidal pressure) and subtracting the free hepatic vein pressure (systemic pressure), thereby obtaining the hepatic venous pressure gradient (HVPG) [1]. A normal HVPG is 3-5 mm Hg. An HVPG greater than 5 mm Hg defines PH. Once the HVPG reaches 10 mm Hg or greater, the patient with compensated cirrhosis is at a higher risk of developing varices [2], clinical decompensation (including variceal hemorrhage) [3], and hepatocellular carcinoma [4]. Therefore, a HVPG of 10 mm Hg or greater has been designated as clinically significant portal hypertension (CSPH). Patients with gastroesophageal varices have an HVPG of at least 11-12 mm Hg and, by definition, have CSPH.

Variceal hemorrhage, a complication that defines decompensation, occurs at an annual rate of 5%-15% in cirrhotic patients. Although mortality from variceal hemorrhage has decreased over the years, its 6-week mortality still remains significant at 10%-20%. Therefore, a key part in the management of patients with varices is to prevent a first episode of variceal bleeding (primary prophylaxis) and, in a patient who has recovered from an episode of hemorrhage, to prevent recurrent variceal bleeding (secondary prophylaxis).

The prevention of variceal hemorrhage had until now been applied to all patients with cirrhosis regardless of clinical stage and presence (or absence) of complications of cirrhosis. As staging of cirrhosis has become clearer, the most recent Baveno consensus conference on PH [5] and practice guidelines on portal hypertensive bleeding in cirrhosis [6] emphasize risk stratification and place the different therapies of PH in the context of the different prognostic stages (PS) and substages of cirrhosis.

2. Prognostic stages (PS) of cirrhosis

Cirrhosis is classified in at least 2 PS, compensated and decompensated, with the compensated stage being the asymptomatic stage and the decompensated stage being the symptomatic stage

The author reports no direct financial interests that might pose a conflict of interest in connection with the submitted manuscript.
Financial support: Yale Liver Center (NIH P30 DK34989).
* Corresponding author.
E-mail address: guadalupe.garcia-tsao@yale.edu (G. Garcia-Tsao).

http://dx.doi.org/10.1016/j.tgie.2017.03.004
0049-0172/

defined by the presence of overt ascites, variceal hemorrhage, or overt hepatic encephalopathy. Substages of compensated and decompensated cirrhosis have recently been identified that are not only of prognostic significance but also of pathophysiological significance [6]. These PS are outlined later in the context of varices and variceal hemorrhage.

2.1. PS-1: Patients with compensated cirrhosis with mild PH (HVPG $>$ 5 mm Hg but $<$ 10 mm Hg)

These patients have a minimal risk of decompensation or death and the main pathophysiological mechanism of PH is increased intrahepatic resistance.

2.2. PS-2: Patients with compensated cirrhosis and CSPH without varices

These patients are at a higher risk of decompensation than those with mild PH, and both increased resistance and flow are pathophysiological mechanisms of PH.

2.3. PS-3: Patients with cirrhosis and gastroesophageal varices that have never bled

These patients have, by definition, CSPH because it has been shown that patients with varices have an HVPG of at least 10-12 mm Hg. They are at a higher risk of decompensation and an increased hyperdynamic state compared with those at the previous stage.

2.4. PS-4: Patients with cirrhosis presenting with acute variceal hemorrhage

Although these patients are, by definition, decompensated, their prognosis depends markedly on the presence or absence of other complications of cirrhosis. Patients with variceal hemorrhage alone have a relatively low-mortality, whereas those who bleed in the presence of other complications of cirrhosis (most commonly ascites) are at high-risk of early rebleeding and death.

2.5. PS-5: Patients with cirrhosis who have recovered from an episode of variceal hemorrhage

These patients are also, by definition, decompensated. However, the objective of treatment depends on the presence or absence of other complications of cirrhosis. An otherwise compensated patient who recovers from a variceal hemorrhage may return to a compensated stage but will be at higher risk of rebleeding and developing another decompensating event (mostly ascites). An already decompensated patient that bleeds has a high-risk of death.

This review focuses on prevention of first variceal hemorrhage (primary prophylaxis) and prevention of recurrent variceal hemorrhage (secondary prophylaxis), in the context of the described stages of PH.

3. PS-1: Patients with compensated cirrhosis and mild PH

The goal of treatment in these patients is to prevent the development of CSPH, which translates in preventing the development of varices and decompensation. The main mechanism of PH in this setting is intrahepatic (increased resistance), which is owing to a combination of structural abnormalities (fibrosis, inflammation, and regenerative nodules) and dysfunction of sinusoidal endothelial cells (SEC) that leads to intrahepatic vasoconstriction. Therefore, therapy is directed toward treating the etiology of cirrhosis and ameliorating SEC dysfunction.

Amelioration of structural abnormalities (and perhaps endothelial dysfunction) includes treating patients for viral hepatitis, abstinence from alcohol in patients with alcoholic cirrhosis, and weight loss in patients with nonalcoholic steatohepatitis cirrhosis. It may also include the use of antifibrotic agents and amelioration of SEC dysfunction. Statins have been shown not only to decrease hepatic fibrogenesis but also to improve SEC dysfunction by increasing nitric oxide bioavailability in experimental animals. In patients with cirrhosis, simvastatin has been shown to decrease HVPG and to improve liver perfusion [7]. In fact, a retrospective propensity score-matched study showed that, in patients with compensated hepatitis C cirrhosis, statin users had a lower incidence of decompensation and death compared with nonusers [8].

As nonselective beta-blockers (NSBB), the most commonly used drugs to reduce portal pressure, act by decreasing portal blood inflow, they are likely ineffective at this stage of cirrhosis as increased portal blood inflow (hyperdynamic circulatory state) that maintains PH is not yet a major pathogenic mechanism [9].

It is essential that any patient with compensated cirrhosis undergoes screening esophagogastroduodenoscopy (EGD), not only to determine the presence of varices that would require prophylactic therapy (described in Section PS-3: patients with compensated cirrhosis and gastroesophageal varices), but also to determine the presence of varices would rule in the presence of CSPH, thereby ruling out mild PH.

4. PS-2: Patients with compensated cirrhosis and CSPH but without varices

This group includes patients with CSPH, defined as HVPG $\geq$ 10 mm Hg, a pressure threshold that predicts the development of varices, decompensation (ascites, hepatic encephalopathy, and variceal hemorrhage), as well as hepatocellular carcinoma [2-4].

Noninvasive methods, in particular liver stiffness $>$ 20-25 kPa as measured by transient elastography, alone or in combination with spleen size or platelet count, are useful to rule in CSPH [5]. Patients who have portosystemic collaterals on cross-sectional imaging, even though they do not have gastroesophageal varices on EGD, have CSPH [5].

The goal of treatment at this stage is to prevent the development of varices as well as clinical decompensation. The main pathogenic mechanisms at this stage include increased intrahepatic resistance and increased portal venous inflow. Therefore, in addition to interventions that act on intrahepatic resistance (treatment of etiology, antifibrotic agents, and statins), reduction of portal venous inflow by NSBB is considered. Although a large multicenter randomized placebo-controlled clinical trial aimed at preventing the development of varices in patients with compensated cirrhosis did not show any difference between NSBB and placebo [2], another multicenter randomized placebo-controlled study aimed at preventing clinical decompensation in patients at PS-2 or PS-3 (with small varices only) stages showed that NSBB (propranolol or carvedilol) were significantly more effective in preventing decompensation (when adjusted for nonliver deaths) and in preventing ascites [10]. Although the latter study has only been presented in abstract form, NSBB use may be considered at this stage.

It is essential that patients with newly diagnosed compensated cirrhosis undergo screening EGD for the presence and size of gastroesophageal varices. This not only serves as the basis for further substaging of patients with CSPH, but also identifies the patient population with high-risk varices that will require prophylaxis for prevention of a first variceal hemorrhage (described in