Primary Prophylaxis of Variceal Bleeding

Jawad A. Ilyas, MD, MS[a], Fasiha Kanwal, MD, MSHS[a,b,*]

KEYWORDS

• Portal hypertension • Cirrhosis • Hemorrhage

KEY POINTS

- Both nonselective beta-blockers and endoscopic band ligation form the cornerstone of prophylactic therapy for varices.
- In the absence of accurate noninvasive markers of hepatic venous pressure gradient, variceal size, high-risk stigmata of variceal bleeding, and the stage of underlying liver disease dictate the choice of prophylactic therapy.
- The major challenge is to screen patients in a timely manner and institute a form of therapy that has the highest chance of success in terms of both compliance and effectiveness.
- Without systematic efforts targeted at reducing these gaps in health care delivery, recent advances in the efficacy of primary prophylaxis may not translate into effective varices care at the bedside.

BACKGROUND

Cirrhosis is a common and burdensome condition. It is responsible for approximately 1 million days of work lost and 32,000 annual deaths in the United States, and thus has a substantial effect on productivity and survival.[1] The high mortality in cirrhosis is attributable, in part, to the development of varices and subsequent hemorrhage. Despite substantial advances in medical management of variceal bleeding, each episode of active variceal bleeding is fatal in 30% of cases.[2,3]

Development of varices is a direct consequence of portal hypertension and reflects abnormal changes in both portal resistance and flow. Portal hypertension is commonly

Funding: This work is partly funded by the Houston Veterans Affairs Health Services Research and Development Center of Excellence HFP90-020.
Disclosures: No conflicts of interest exist.
Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.
[a] Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, 6620 Main St., Houston, TX 77030, USA; [b] Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA
* Corresponding author. 2002 Holcombe Boulevard, Houston, TX 77030.
E-mail address: kanwal@bcm.edu

Gastroenterol Clin N Am 43 (2014) 783–794
http://dx.doi.org/10.1016/j.gtc.2014.08.008 **gastro.theclinics.com**
0889-8553/14/$ – see front matter Published by Elsevier Inc.

measured using the hepatic venous pressure gradient (HVPG), which is the difference between wedged and free hepatic venous pressure. Varices generally develop when the hepatic venous pressure gradient (HVPG) exceeds 5 to 10 mm Hg as a compensatory mechanism to decompress the portal system; variceal bleeding occurs when the HVPG exceeds 12 mm Hg.[4] Esophageal varices are present in approximately 40% of patients with cirrhosis and as many as 60% of patients with cirrhosis and ascites. In patients without varices, new varices develop at the rate of 5% to 8% per year.[4] In patients with small varices at the time of initial endoscopic screening, progression to large varices occurs at a rate of 10% to 15% per year.[4] One of the largest prospective studies that followed the natural history of variceal progression enrolled 206 patients with cirrhosis. Of these, 113 patients did not have varices at baseline and 93 patients had small varices. After an average follow-up of 37 months, 28% of patients (without varices) developed varices, whereas 31% of patients (with small varices) experienced progression in variceal size. The strongest predictors of progression were the Child-Pugh score at baseline, presence of stigmata of bleeding (red wale markings), baseline platelet count, and alcohol-related liver disease. The risk of variceal bleeding was significantly higher in the patients who had small varices at baseline compared with those who did not have varices (12% vs 2% at 2 years).[5] A more recent study using data from the HALT-C trial found a similar rate of de novo varices development and progression (26.2% and 35.3%, respectively) during a median follow-up of 48 months.[6] Hispanic race and lower baseline albumin level were both strongly associated with the risk of varices development.

Several clinical and physiologic factors are associated with the risk of first variceal hemorrhage. These include variceal location, size, appearance of the varices, underlying HVPG, and the degree of hepatic dysfunction.[1] Of these, HVPG is the most important and a potentially modifiable risk factor. HVPG serves as an accurate surrogate marker of variceal development, as well as the risk of variceal bleeding. In a systematic review of prospective studies, a reduction in the HVPG to 12 mm Hg or lower, or a reduction of 20% or more from baseline significantly reduced the risk of first variceal bleeding (pooled odds ratio 0.21, 95% confidence interval [CI] 0.05–0.80).[7] Therapies aimed at reducing the HVPG below this threshold can affect the progression of varices and reduce the risk of first variceal bleeding.

PRIMARY PROPHYLAXIS

Prophylaxis is derived from the Greek word *prophulaktikos*, meaning "prevention." Primary prophylaxis entails prevention of the first episode of variceal bleeding after diagnosis of varices. However, this concept can be expanded to (1) prevention of formation of varices (preprimary prophylaxis), (2) prevention of progression of variceal size (early-primary prophylaxis), and (3) prevention of the first episode of bleeding (primary prophylaxis).

SCREENING FOR VARICES

Although the point prevalence of varices in patients with cirrhosis is relatively high, most patients with cirrhosis may not have varices. As a result, guidelines recommend screening for the presence of varices in patients with cirrhosis[8–10] and initiating treatment targeted at primary prophylaxis for patients identified to have high-risk varices.

Esophagogastroduodenoscopy (EGD) is considered the gold standard for the diagnosis of varices. However, EGD is relatively expensive and requires specialized expertise to perform. Moreover, as mentioned previously, most patients undergoing EGD either do not have varices or have varices that do not require prophylactic treatment