REVIEW

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Preventing a first episode of esophageal variceal hemorrhage

ABSTRACT

In patients with esophageal varices, hemorrhage is common and often lethal, so we need to take a proactive approach to preventing a first episode of bleeding. All patients with cirrhosis should undergo endoscopy to look for varices. Depending on the size and appearance of the varices and the patient's Child-Pugh grade, prophylactic treatment may be indicated.

KEY POINTS

The hepatic vein pressure gradient (HVPG) correlates well with the portal pressure and is easier to measure. However, whether it is cost-effective to measure the HVPG in clinical practice is controversial.

Nonselective beta-blockers are the mainstay of treatment; selective beta-blockers do not reduce portal pressure to the same degree and are not recommended for preventing variceal bleeding.

Endoscopic variceal ligation is an acceptable alternative to beta-blocker therapy for patients who cannot tolerate these drugs and for patients with varices at high risk of bleeding.

Nitrates are no longer used as monotherapy for preventing variceal hemorrhage, and their use in combination with beta-blockers is controversial. Surgical portal decompression, transjugular intrahepatic portosystemic shunting, and endoscopic sclerotherapy are not recommended.

VARICEAL HEMORRHAGE is a medical emergency in which up to 20% of patients die.[1] Even if the patient survives an initial episode of variceal bleeding, the probability of another episode is high: the rebleeding rate without treatment is 70% within 1 year. The mortality rate with rebleeding is 33%.

With such overwhelming consequences, the best strategy in any patient with cirrhosis and known varices is to try to prevent the first episode of bleeding.

WHO IS AT RISK?

Esophageal varices are present in 30% of patients with compensated cirrhosis and in up to 60% of those with decompensated cirrhosis (ie, with evidence of ascites or encephalopathy).[2]

The risk of variceal hemorrhage is related to three factors:

- **The size of the varices.** Varices 5 mm in diameter or smaller have a 7% risk of bleeding in 2 years, while those larger than 5 mm have a 30% risk of bleeding within 2 years.[3]
- **The appearance of the varices.** Morphologic features of varices, including red wale signs (red streaks of the mucosa overlying the varix), have been correlated with an increased risk of hemorrhage.
- **The severity of liver dysfunction,** as assessed by the Child-Pugh classification—an index of liver dysfunction based on serum albumin concentration, bilirubin level, prothrombin time, and the presence of ascites and encephalopathy. A high Child-Pugh score (ie, class B or C), representing decompensated cirrhosis, is associated with an increased risk of bleeding.

HOW VARICES DEVELOP: PORTAL HYPERTENSION

Esophageal varices form as a result of increased portal pressure, the product of increased portal venous inflow and resistance to outflow from the portal venous system. Portal hypertension is a major complication of chronic liver disease. In cirrhosis, architectural distortion of the liver causes an increase in the intrahepatic vascular resistance.

Portal venous inflow depends on mesenteric arteriolar tone, increasing when tone decreases. In cirrhotic patients, the increase in portal pressure results from a combination of increased portal blood flow secondary to splanchnic arteriolar vasodilation and elevated resistance to outflow through distorted hepatic sinusoids.

The potent vasodilator nitric oxide (NO) plays an important role in portal hypertension. In patients with cirrhosis, NO bioavailability is decreased in the intrahepatic circulation due to defects in the posttranslational regulation of endothelial NO synthase.[4] This deficiency of NO, along with mechanical factors in the sinusoids, contributes to the increase in intrahepatic resistance. In the systemic and splanchnic circulation, NO bioavailability is increased due to upregulation and posttranslational regulation of endothelial NO synthase, thereby increasing splanchnic vasodilatation and leading to increased portal venous inflow.[5] This results in a marked increase in cardiac output and so-called hyperdynamic circulation.

Varices do not bleed if the HVPG is less than 12 mm Hg

Portal hypertension results in the development of collateral circulation, including venous channels in the esophagus and stomach, by the dilation of preexisting vessels and active angiogenesis. Esophagogastric varices increase in size with the severity of portal hypertension and can rupture when the tension in their walls exceeds a maximal point.

HEPATIC VEIN PRESSURE GRADIENT: A PROXY FOR PORTAL PRESSURE

Ideally, the portal venous pressure should be directly measured. However, since direct measurement is invasive and impractical, the hepatic vein pressure gradient (HVPG) can be measured instead and correlates well with the portal pressure.[6]

The HVPG is measured by catheterizing the hepatic vein via a transfemoral or transjugular route. The small catheter is threaded into the hepatic vein until it cannot be advanced any further, and a "wedged" hepatic venous pressure is obtained (**FIGURE 1**). Alternatively, a balloon-tipped catheter can be used to occlude a larger hepatic venule.[7] The HVPG is equal to the wedged hepatic venous pressure (which reflects portal venous pressure) minus the free hepatic venous pressure (which reflects intra-abdominal pressure).

The normal HVPG is 5 mm Hg or less; anything above this value denotes portal hypertension. However, studies have shown that varices may develop but do not bleed if the HVPG is less than 12 mm Hg.[8]

TWO WAYS TO PREVENT BLEEDING

Bleeding can be prevented either by reducing the portal venous pressure or by obliterating the varices. Portal pressure can be reduced by placing a portosystemic shunt either surgically or percutaneously with radiographic guidance or by giving drugs such as nonselective beta-blockers, nitrates, or a combination of these drugs. Variceal obliteration is typically done by endoscopic methods with either injection of a sclerosant or band ligation.

NONSELECTIVE BETA-BLOCKERS: THE MAINSTAY OF TREATMENT

Nonselective beta-blockers, the most commonly used drugs for preventing first esophageal variceal bleeding, decrease portal pressure by blocking both beta-1 and beta-2 adrenergic receptors.[9] Beta-1 blockade decreases portal flow by decreasing the heart rate and cardiac output, while blockade of beta-2 receptors results in unopposed alpha-adrenergic-mediated vasoconstriction.

Selective beta-blockers do not appear to be as useful for primary prophylaxis. More than 2 decades ago, metoprolol (Toprol, Lopressor), a beta-1 selective antagonist, was compared with propranolol (Inderal), a nonselective agent, in patients with cirrhosis and

How liver disease leads to bleeding varices

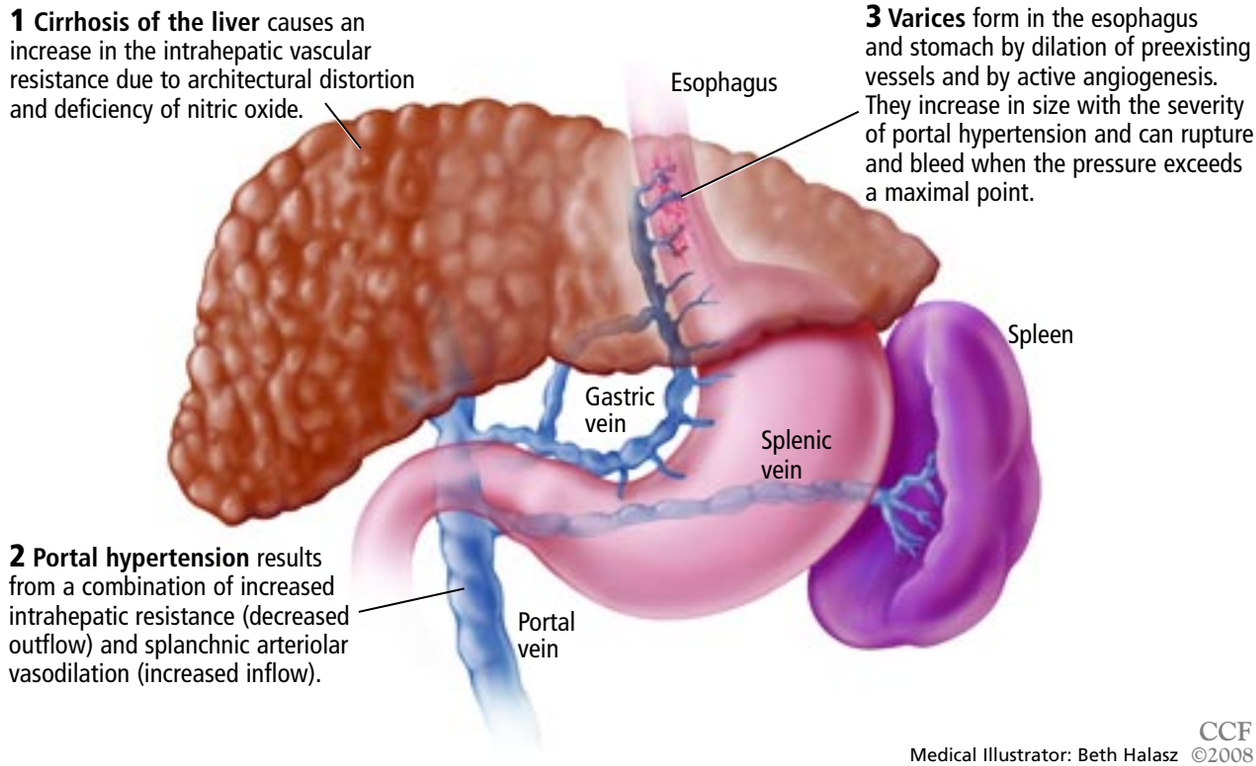

FIGURE 1

portal hypertension.[10] Although both drugs significantly reduced the heart rate and cardiac output, only those taking propranolol showed a marked fall in portal pressure (mean decrease of 6.8 mm Hg vs 3.8 mm Hg with metoprolol) and a significant reduction in hepatic blood flow. The differences were thought to be related to beta-2 blockade of vasodilator receptors in the splanchnic circulation, which occurs only with nonselective beta-blockers such as propranolol.

The two nonselective beta-blockers most often used to prevent variceal bleeding are nadolol (Corgard) and propranolol. Both have been extensively studied in preventing a first variceal hemorrhage.

Effectiveness of beta-blockers

D'Amico et al[11] performed a meta-analysis in 1995, examining nine trials (996 patients total) of the effectiveness of beta-blockers in preventing a first variceal hemorrhage. Seven trials found that bleeding risk was reduced with beta-blockers (significantly in four), one trial found that risk was unchanged, and one trial found that risk was increased—an outlier due to a small sample size. The meta-analysis showed a significant bleeding reduction with the use of a beta-blocker, either including the outlier trial (pooled odds ratio 0.54; 95% confidence interval 0.39–0.74) or excluding it (pooled odds ratio 0.48; 95% confidence interval 0.35–0.66).

Mortality rates were also reduced in seven trials, but the reduction was statistically significant in only one. However, in the pooled estimate, the mortality risk reduction approached statistical significance (pooled odds ratio 0.75; 95% confidence interval 0.57–1.06).

Ideo et al[12] gave either nadolol or placebo to 79 patients with cirrhosis and large esophageal varices that had never bled. Nadolol was found to protect against a first variceal hemorrhage: at 2-year follow-up, only 1 of the 30 patients allocated to nadolol had

had bleeding, vs 11 of the 49 patients in the placebo group.

Merkel et al[13] found that the risk of variceal bleeding was lower in patients who started treatment with beta-blockers when their varices were small (12% at 5 years) than in those who started treatment after a diagnosis of large esophageal varices (22% at 5 years). They concluded that nadolol helps prevent small varices from growing into larger ones.

Response to beta-blockers is not uniform

Although beta-blockers decrease the portal pressure in many cirrhotic patients, the response is not uniform. In a study of 60 cirrhotic patients,[14] 40% showed no reduction or even a slight increase in HVPG with propranolol. Most patients showed a significant reduction in heart rate (17.5% ± 10%) after receiving 40 mg of propranolol. In the patients whose HVPG did not decrease by at least 10% with 40 mg of propranolol, increasing the dose caused a decrease in HVPG without a further decrease in heart rate. This suggests that 40 mg of propranolol successfully produced beta-1 blockade but that a higher dose was required for effective beta-2 blockade.

Lower doses of beta-blockers may reduce peripheral blood pressure but not portal pressure

Failure to respond in certain patients may be due to a concurrent rise in collateral or hepatic sinusoidal resistance, or both. This was confirmed in a study in portal-hypertensive rats treated with propranolol.[15] The reduction in portal blood flow expected was accompanied by a disproportionately small reduction in portal pressure, which was thought to be due to a rise in portal and collateral vascular resistance.

How to tell if beta-blocker treatment is 'working'

An HVPG ≤ 12 mm Hg? Studies have shown that the most important predictor of efficacy of prophylaxis for variceal bleeding is a decrease in the HVPG to 12 mm Hg or less or a decrease in the initial HVPG of more than 20%.[9] Although measuring the HVPG is invasive, expensive, and not routinely done in clinical practice, several studies have investigated the role of measuring hemodynamic response to medication.

Merkel et al[16] measured the HVPG in 49 cirrhotic patients with previously nonbleeding varices before starting therapy with beta-blockers with or without nitrates and after 1 to 3 months of treatment. They followed the patients for up to 5 years. The mean HVPG value at baseline was 18.8 mm Hg. At 3 years of follow-up, 7% of those who had responded well to therapy (defined as achieving an HVPG less than 13 mm Hg or a decrease of more than 20%) had experienced a bleeding episode, which was significantly less than the rate (41%) in those who did not meet those hemodynamic end points. No patient reaching an HVPG of 12 mm Hg or less during treatment had variceal bleeding during follow-up.

Groszmann et al[17] also prospectively measured the HVPG in patients with cirrhosis and varices, but their patients received either propranolol or placebo. Variceal hemorrhage occurred in 13 patients (11 of 51 in the placebo group and 2 of 51 in the propranolol group), all of whom had an HVPG greater than 12 mm Hg. Again, none of the patients whose HVPG was decreased to 12 mm Hg or less bled from esophageal varices.

Unfortunately, routine HVPG measurement to guide primary prophylaxis is an expensive strategy. Data suggest that measuring the HVPG is cost-effective only when the cost of measuring the HVPG is very low, the risk of variceal bleeding is very high, or the patient is expected to survive at least 3 to 5 years.[18]

A heart rate of 55 to 60? An alternative to HVPG measurement to monitor the effectiveness of beta-blocker therapy is to follow the heart rate. A 25% reduction from baseline or a heart rate of 55 to 60 beats per minute is the standard goal[19,20]; yet, at least 40% of patients treated with enough propranolol to decrease the heart rate by 25% do not respond with significant HVPG reductions.[14,21]

So, although beta-blockade is effective peripherally, it may not reduce HVPG to less than 12 mm Hg or 20% from baseline, and direct HVPG measurement is still the gold standard.

Treatment should be lifelong

Once a patient is started on a beta-blocker to prevent variceal hemorrhage, the treatment should be lifelong.

In 2001, a group of patients (most of them in Child-Pugh class A or B) completing a prospective randomized controlled trial of propranolol for primary prevention of variceal hemorrhage were tapered off propranolol or placebo.[22] Of the 49 patients, 9 experienced variceal hemorrhage (6 of 25 former propranolol recipients and 3 of 24 former placebo recipients), and 17 patients died (12 former propranolol and 5 former placebo recipients), suggesting that treatment should be maintained for life.

Therefore, when beta-blocker therapy is discontinued, the risk of variceal hemorrhage returns to what would be expected in an untreated population.

Beta-blockers may not prevent varices

Although many trials have shown that beta-blockers are effective as prophylaxis against a first variceal hemorrhage, there is no evidence that these drugs prevent varices from forming in cirrhotic patients.

Groszmann et al[23] treated more than 200 patients who had biopsy-proven cirrhosis and portal hypertension (HVPG > 6 mm Hg) but no varices with timolol (Blocadren), a nonselective beta-blocker, or placebo. At a median follow-up of about 55 months, the groups did not differ significantly in the incidence of primary events (development of varices or variceal hemorrhage) or treatment failures (transplantation or death). Varices developed less frequently among patients with a baseline HVPG of less than 10 mm Hg and among those whose HVPG had decreased by more than 10% at 1 year. In patients whose HVPG increased by more than 10%, varices developed more frequently.

Contraindications, side effects

The major drawbacks to therapy with beta-blockers are their contraindications and side effects.

Contraindications include chronic obstructive lung disease, psychosis, atrioventricular heart blocks, and aortic-valve disease.

Side effects are reported in 15% of patients but severe events are rare.[24] Still, an estimated 10% to 20% of patients discontinue treatment because they cannot tolerate it.[25] The more common complaints include fatigue, shortness of breath, sexual dysfunction, and sleep disorders.

Dosage

No specific starting dose of beta-blockers is agreed upon, but nadolol 20 to 40 mg once daily or long-acting propranolol 60 mg once daily can be used as initial therapy.[25] Once-daily dosing increases the likelihood of compliance.

Since portal pressure progressively declines from 12 noon to 7 PM and then increases throughout the night and back to baseline by 9 AM,[26] we recommend that the medication be taken in the evening to counteract increases in portal pressure that occur in the middle of the night.

ENDOSCOPIC VARICEAL LIGATION

Endoscopic variceal ligation has been investigated extensively for use as prophylaxis against first variceal hemorrhage. The procedure involves placing a rubber band around a varix aspirated into a cylinder on the tip of an endoscope.

Effectiveness of ligation

Lay et al,[27] in a prospective, randomized trial in 126 cirrhotic patients endoscopically judged to be at high risk of hemorrhage, found that ligation significantly reduced the 2-year cumulative bleeding rate (19% with ligation vs 60% in an untreated control group) and the overall mortality rate (28% vs 58%). The lower risk of bleeding in the ligation group was attributed to a rapid reduction of variceal size; 60% of those in the ligation group had complete eradication of varices and 38% had varices reduced in size.

Imperiale and Chalasani[28] performed a meta-analysis in 2001 that included 601 patients in five trials comparing prophylactic ligation with untreated controls and 283 patients in four trials comparing ligation with beta-blocker therapy. Compared with no treatment, ligation reduced the risk of first variceal hemorrhage, bleeding-related death, and death from any cause. Compared with propranolol, ligation reduced the risk of first-time bleeding but had no effect on the death rate.

Nonselective beta-blockers lower portal pressure better than selective beta-blockers and therefore are used to prevent variceal bleeding

Schepke et al,[29] in a randomized controlled multicenter trial in 152 cirrhotic patients with two or more esophageal varices, found that neither bleeding incidence nor death rate differed significantly between ligation and propranolol.

Lui et al[30] followed 172 cirrhotic patients with grade II or III esophageal varices for 6 years and found that ligation was equivalent to propranolol. However, many patients reported side effects with propranolol, and 30% of patients withdrew from propranolol treatment, making ligation a more attractive option.

Khuroo et al[31] performed a meta-analysis of eight randomized controlled trials including 596 patients and found that ligation significantly reduced the rates of first gastrointestinal hemorrhage by 31% and of first variceal hemorrhage by 43%. In subgroup analysis, ligation had a significant advantage compared with beta-blockers in trials with patients with a high bleeding risk, ie, trials in which more than 30% of patients were in Child-Pugh class C and more than 50% of the patients had large varices.

When beta-blockers are stopped, the risk of bleeding increases back to baseline

Jutabha et al[32] performed a multicenter, prospective trial (published in 2005) in 62 patients with high-risk esophageal varices randomized to propranolol or banding. The trial was ended early after an interim analysis showed that the failure rate of propranolol was significantly higher than that of banding (6/31 vs 0/31, $P = .0098$). Esophageal variceal hemorrhage occurred in 4 (12.9%) of the patients in the propranolol group compared with 0 in the ligation group. Similarly, 4 patients in the propranolol group died, compared with 0 in the ligation group. All the patients in this trial were liver transplant candidates and therefore all had severe liver disease.

In another trial favoring variceal banding over beta-blockers, Psilopoulos et al[33] in 2005 followed 60 patients with cirrhosis and esophageal varices with no history of bleeding. Thirty percent of the patients in the propranolol group developed variceal bleeding compared with 6.7% in the ligation group ($P = .043$).

Lay et al[34] followed 100 cirrhotic patients for 2 years and found comparable cumulative bleeding rates with ligation vs propranolol (18% vs 16%, respectively) and also comparable rates of death (28% vs 24%, respectively).

Sarin et al[35] investigated the role of propranolol in addition to ligation in the prevention of first hemorrhage in 144 patients. Adding propranolol did not further decrease the incidence of initial bleeding (7% in the combination group vs 11% in the ligation-only group). Survival rates were similar at 20 months: 92% in the combination group vs 85% in the ligation-only group. However, the rate of variceal recurrence was lower with combination therapy: 6% in the combination group vs 15% with ligation alone.

Does esophageal variceal ligation increase gastric varices?

A less researched topic is whether variceal ligation results in gastric hemodynamic changes that increase the size of fundal varices and worsen portal hypertensive gastropathy.

Yuksel et al[36] found that 37 of 85 patients had fundal varices before they underwent ligation of esophageal varices, increasing to 46 after the procedure, a statistically significant increment. The severity of portal hypertensive gastropathy also increased.

Further research is required regarding the long-term consequences of these findings.

ANGIOTENSIN II RECEPTOR ANTAGONISTS: ROLE UNKNOWN

Angiotensin II increases portal pressure, and angiotensin II levels are elevated in patients with cirrhosis, suggesting that this hormone plays a role in the pathogenesis of portal hypertension.

Losartan (Cozaar), an angiotensin II receptor antagonist, was found to decrease the HVPG significantly in patients with severe and moderate portal hypertension in a pilot study[37] in 1999. However, in two subsequent studies,[38,39] losartan only moderately reduced the HVPG and caused hypotension and a reduction in the glomerular filtration rate. The role of angiotensin II receptor blockers in primary prevention of variceal bleeding is still unknown.

SURGICAL PORTAL DECOMPRESSION HAS BEEN ABANDONED

The first method investigated to prevent variceal bleeding was surgical portal decompression.

A meta-analysis of four randomized controlled trials in 302 patients with varices of all sizes compared portocaval shunt surgery and medical therapy.[11] Although shunt surgery was very effective in preventing variceal bleeding, the risk of chronic or recurrent encephalopathy was significantly increased (odds ratio 2.0), as was the risk of death (odds ratio 1.6).

These poor results, combined with advances in endoscopic procedures, led to the abandonment of surgical shunting for primary prophylaxis.

TIPS PROCEDURE: NO ROLE AT PRESENT

The transjugular intrahepatic portosystemic shunt (TIPS) procedure is used to treat the main consequences of portal hypertension, including ascites and variceal hemorrhage. The procedure entails accessing the hepatic vein via the right jugular vein and placing a stent to the portal vein, forming a low-resistance channel and allowing blood to return to the systemic circulation.

TIPS placement increases the risk of encephalopathy; liver failure is a rare complication, and procedural complications (ie, shunt dysfunction) also occur. Trials comparing the TIPS procedure with other forms of therapy to prevent first variceal hemorrhages have not been performed.[40] Research to improve the outcome of the TIPS procedure is ongoing, but currently this procedure has no role in primary prevention of variceal bleeding.

ENDOSCOPIC SCLEROTHERAPY MAY INCREASE THE RISK OF DEATH

Numerous clinical trials evaluated sclerotherapy as prophylaxis against a first esophageal variceal hemorrhage. The procedure involves injecting a sclerosant in and around varices.

In a large Veterans Administration study,[41] sclerotherapy was compared with sham treatment in 281 men with alcoholic liver disease who had documented varices but no history of bleeding. The trial was terminated after 22.5 months because the rate of all-cause mortality was significantly higher in the sclerotherapy group (32.5%) than in the sham therapy group (17.4%). The higher death rate did not persist after the treatment was discontinued, and it was speculated that, although sclerotherapy had reduced new episodes of variceal hemorrhage, the procedure might have caused bleeding from esophageal ulcers, leading to an increased mortality rate in that group.

The PROVA Study Group from Norway and Denmark found similar results when 286 cirrhotic patients were randomized to receive sclerotherapy, propranolol, combination sclerotherapy and propranolol, or no treatment to prevent a first variceal hemorrhage.[42] The incidence of variceal bleeding was almost identical in the four groups, but the mortality rate with variceal bleeding was 2.75 times higher in the sclerotherapy groups than in the other groups ($P = .002$). It was speculated that repeated sclerotherapy sessions might be poorly tolerated by patients in Child-Pugh classes B and C and might have contributed to the precipitation of liver failure and other common complications of cirrhosis.

A meta-analysis by D'Amico et al[11] evaluated 19 trials (1,630 patients) comparing sclerotherapy with nonactive treatment. Sclerotherapy tended to be favorable in trials with a high bleeding rate in the control patients and unfavorable in trials with a low bleeding rate. The benefit seen in patients at high risk is consistent with the efficacy of sclerotherapy for preventing rebleeding, whereas the harmful effect in the low-risk patients points towards side effects and complications exceeding the potential benefits.

Varices grow at a rate proportional to the severity of the liver disease

In general, currently available evidence suggests that the benefits of prophylactic sclerotherapy are marginal, and therefore sclerotherapy is not recommended as primary prophylaxis for variceal hemorrhage.

NITRATES: NO LONGER USED AS MONOTHERAPY

Unlike vasoconstrictors, which decrease portal pressure by decreasing blood flow, vasodilators reduce hepatic pressure by decreasing intrahepatic and portocollateral vascular resistance.[43] In addition, larger doses directly affect the arterial circulation, lowering sys-

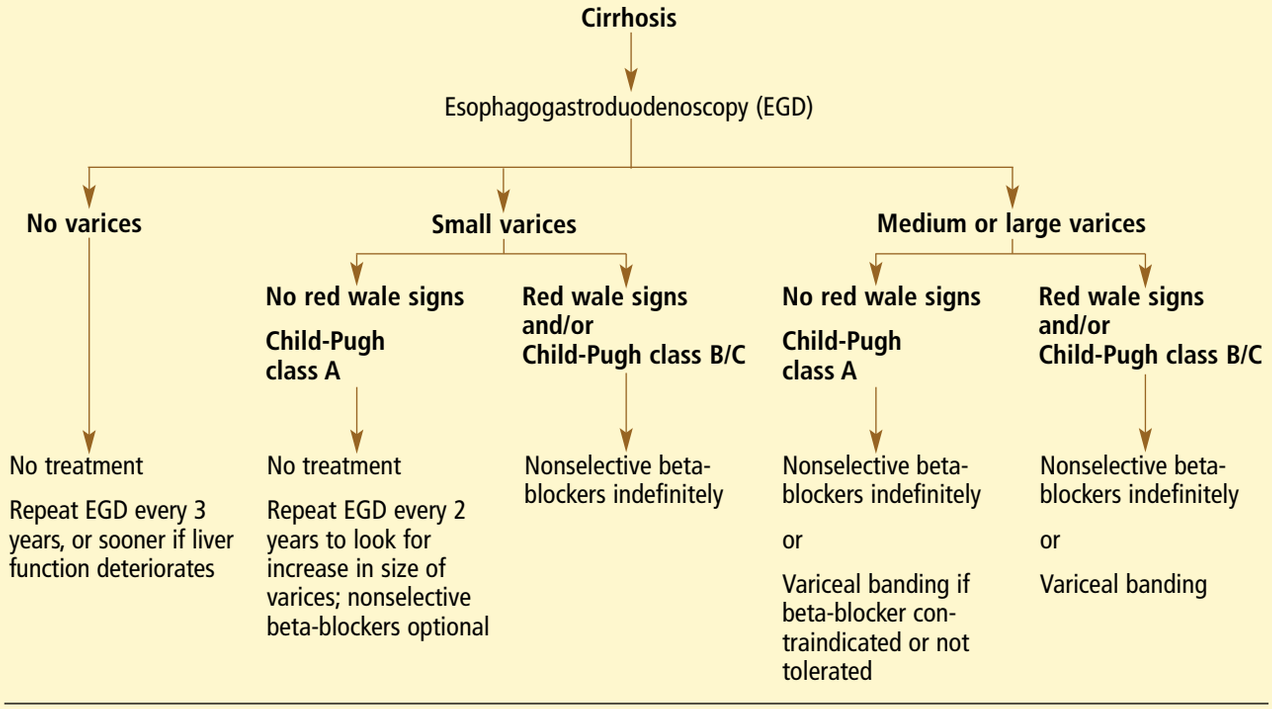

FIGURE 2. Practice guidelines

BASED ON GARCIA-TSAO G, SANYAL A, GRACE N, ET AL. PREVENTION AND MANAGEMENT OF GASTROESOPHAGEAL VARICES AND VARICEAL HEMORRHAGE IN CIRRHOSIS. HEPATOLOGY 2007; 46:922–938.

temic and therefore splanchnic perfusion pressure.[44] Unfortunately, the systemic vasodilatory effects of nitrates exacerbate the hyperdynamic state that is characteristic of cirrhosis, thereby limiting their use and tolerability in many patients.

A trial comparing propranolol vs isosorbide mononitrate initially found that the groups did not differ significantly with regard to bleeding rates and 2-year survival rates,[45] but a 6-year follow-up found the likelihood of death greater in patients older than 50 years in the nitrate group.[46] In an additional study comparing isosorbide mononitrate vs placebo in patients with contraindications to or intolerance of beta-blockers, no difference in the relative risk of first variceal hemorrhage was found between the two groups.[47] Therefore, nitrates are no longer used as monotherapy to prevent variceal bleeding.

Combination therapy with beta-blockers plus nitrates is controversial. In a trial in 1996, Merkel et al[48] found the cumulative risk of variceal bleeding was 18% at 40 months with nadolol alone vs 7.5% with nadolol plus isosorbide mononitrate. However, in a later trial, Garcia-Pagán et al[49] found no significant advantage to combination therapy. The incidence of variceal bleeding at 1 year was 8.3% in the group receiving propranolol plus placebo and 5% in the group receiving propranolol plus isosorbide mononitrate; at 2 years, the rates were 10.6% vs 12.5%.

RECOMMENDATIONS FOR SCREENING AND PROPHYLAXIS

Formal guidelines regarding appropriate prophylaxis against a first variceal hemorrhage have recently been published.[50] The following recommendations include those covered in the guidelines (FIGURE 2):

- All patients with cirrhosis should be screened for varices at the time of diagnosis.
- The size of the varices, including small (≤ 5 mm) and large (> 5 mm), and the presence of red wale marks on the varices should be recorded.

- Patients who have no varices on screening endoscopy should be rescreened every 3 years if their liver function is stable or every year if their liver function deteriorates. (Varices grow at a rate proportional to the severity of the liver disease.)
- Patients with portal hypertension but without varices do not need treatment with nonselective beta-blockers. Endoscopy should be performed at the intervals suggested above.
- Those who are found to have small varices on screening endoscopy but who have well-compensated liver disease (Child-Pugh class A) and no red wale marks should be rescreened every other year because the development of large varices is greater in patients with small varices on initial endoscopy than in patients with no varices. Emerging data support the use of beta-blockers to prevent varices from increasing in size.
- Patients who have small varices with red wale signs or who are in Child-Pugh class B or C have an increased risk of bleeding and should be treated with beta-blockers. If beta-blockers are not used, endoscopy should be done every year to look for an increase in variceal size.
- Patients who have large varices without red wale signs or who are in Child-Pugh class B or C should be treated with nonselective beta-blockers. The dose should be adjusted to achieve maximal tolerable decrease in heart rate to a minimum of 55 beats per minute, and treatment should be continued indefinitely.
- Endoscopic variceal ligation is an acceptable alternative to beta-blocker treatment as first-line therapy in those who cannot tolerate beta-blockers or who have contraindications to their use, or in those who have red wale marking or who are in Child-Pugh class B or C. ■

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