ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Overview of Current Management of Portal Hypertension

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G&H Currently, what are the most common causes of portal hypertension?

GG-T Portal hypertension is high pressure in the portal vein, which is the vein that carries blood to the liver. By far, the most common cause of portal hypertension is cirrhosis. Normally, the liver is a soft organ, and blood flows through it very easily. With cirrhosis, the liver becomes hard and blood cannot flow easily, so it backs up and pressure increases in the portal vein.

The second most common cause is portal vein thrombosis, when there is a clot in a part of the portal vein before the liver. This results in a prehepatic type of portal hypertension. The liver is healthy, but the clot is an obstruction, and pressure increases in the portion of the portal vein that is proximal to the clot. In cirrhosis, the obstruction is the liver itself.

G&H How do patients with portal hypertension typically present?

GG-T A typical presentation involves varices or variceal bleeding. Vessels in the esophagus, known as varices, normally carry blood into the portal system, but with portal hypertension, these vessels enlarge and carry blood away from the portal vein. These vessels may rupture, causing the patient to vomit blood. A more common, but more ominous, presentation of cirrhosis with portal hypertension is the development of fluid in the abdomen, referred to as ascites. Once the patient presents with variceal bleeding or ascites, the patient's cirrhosis has decompensated.

G&H How is portal hypertension currently measured?

GG-T All of the research to date has measured portal pressure by determining the hepatic venous pressure gradient (HVPG), although this approach is invasive. A needle is placed in the jugular vein, and pressure is measured in the liver sinusoids. This indirect measure is used because accessing the portal vein directly is very difficult.

G&H What is the current understanding of clinically significant portal hypertension?

GG-T Clinically significant portal hypertension is defined as an HVPG equal to or higher than 10 mm Hg, mild portal hypertension as 6 to less than 10 mm Hg, and normal pressure as 3 to 5 mm Hg. Patients with mild portal hypertension are unlikely to decompensate, whereas patients with clinically significant portal hypertension are more likely to decompensate (ie, they develop ascites; bleed from varices; or develop encephalopathy, which is when ammonia is not cleared by the liver because it escapes through collateral veins, causing the patient to become confused).

G&H Have there been any recent changes in the treatment paradigm of patients with cirrhosis and portal hypertension?

GG-T There may now be a new treatment approach. In the past, when cirrhosis was diagnosed, the next step

was to perform an endoscopy to determine whether the patient had varices. Patients with large varices were treated via banding of the varices or with nonselective beta blockers because the varices were likely to bleed. The main goal was to prevent variceal hemorrhage, and no measures were used to prevent the other 2 decompensating events, ascites or encephalopathy. A seminal randomized, placebo-controlled study was published last year, the PREDESCI trial, which showed that nonselective beta blockers prevent decompensation (mainly ascites) in patients with clinically significant portal hypertension. This concept will likely lead to a paradigm shift. Now, when a diagnosis of cirrhosis is made, the next step is to determine whether the patient has clinically significant portal hypertension and, if so, to start nonselective beta blockers to prevent decompensation.

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G&H How effective are nonselective beta blockers in patients with portal hypertension?

GG-T These agents are very effective, although they do not decrease portal pressure in all patients. In the PREDESCI trial, investigators used the beta blockers propranolol and carvedilol and adjusted their doses based on heart rate and blood pressure. Carvedilol is a much more potent nonselective beta blocker because it has additional alpha-adrenergic blocking effects. In the trial, one-third of patients received carvedilol, while two-thirds received propranolol. Patients who received carvedilol had a greater portal pressure–reducing effect and had better outcomes.

G&H What have other studies reported thus far regarding which nonselective beta blocker is most effective in this setting?

GG-T Several investigational studies have shown that carvedilol is more effective than propranolol at lowering HVPG. However, carvedilol lowers the mean arterial pressure much more than propranolol. Thus, if an individual taking carvedilol has low blood pressure, as is often the case with a decompensated patient, he or she is more likely to become hypotensive. This is the main concern with using carvedilol. On the other hand, there is no issue with carvedilol use in compensated patients, as their blood pressure is typically normal.

G&H What is the current role of portosystemic shunting procedures in patients with portal hypertension?

GG-T It is important to emphasize that portosystemic shunts such as the transjugular intrahepatic portosystemic shunt (TIPS) procedure should never be used in compensated patients, as this will divert blood flow away from the liver and could actually lead to decompensation in a patient who is otherwise doing well. In contrast, decompensated patients may need to urgently decompress portal pressure because they may be bleeding massively from varices. In these decompensated patients, the TIPS procedure could be life-saving.

G&H When should the TIPS procedure be used in decompensated patients?

GG-T In general, the TIPS procedure is second-line therapy for variceal hemorrhage or ascites in patients with decompensated cirrhosis. That is, it is performed when bleeding or ascites are not responding to standard of care. Having said that, doctors probably have been waiting too long to use the TIPS procedure. It should not be used too late, but it should also not be used too early, when it may divert blood flow away from the liver. The ideal timing is still being debated. I think doctors are starting to consider the TIPS procedure earlier on now. I would not wait for a patient to bleed for the third time; once a patient bleeds a second time, I would turn to the TIPS procedure. The current indications and timing of the TIPS procedure were recently discussed at an expert consensus conference by the ALTA (Advancing Liver Therapeutic Approaches) Consortium and are expected to be published soon.

G&H Does there appear to be a role for statins in the management of portal hypertension?

GG-T Statins can dilate the vessels that are inside the liver and that are constricted. There are experimental studies and proof-of-concept studies in patients with cirrhosis showing that statins lower portal pressure while improving flow to the liver. However, there is a lack of

randomized clinical trials that show that statins can prevent decompensation. There is currently an ongoing multicenter, randomized, controlled Veterans Affairs study investigating the use of statins in compensated cirrhosis with the objective of preventing decompensation. The National Institutes of Health has recently announced a research project cooperative agreement looking at trials on statins for this use.

G&H What other research is being conducted in this field?

GG-T As previously mentioned, measurement of HVPG is invasive. Many investigations are looking at noninvasive methods to determine who has or does not have clinically significant portal hypertension. For example, some research is examining noninvasive assessment of liver stiffness because the stiffer the liver, the higher the portal pressure. Another method being studied to determine whether a patient has clinically significant portal hypertension is measuring the platelet count in combination with liver stiffness measurement.

In addition to looking for other ways of reducing portal pressure, there has also been much discussion on the preemptive use of the TIPS procedure. This involves placement of the TIPS procedure in patients admitted with variceal bleeding who respond to standard of care but are at a high risk of rebleeding during the admission. In these patients, rather than wait to use the TIPS procedure when the patient rebleeds, it would be used preemptively. There is controversy over which patients are candidates for doing this, so further research is needed.

Finally, we are looking forward to the upcoming Baveno VII Consensus Conference, which will take place in less than a year. New guidelines will be developed for portal hypertension that will include the use of nonselective beta blockers in patients with clinically significant portal hypertension (without having to perform an endoscopy) and the indications for preemptive use of the TIPS procedure.

Disclosures

Dr Garcia-Tsao has no relevant conflicts of interest to disclose.

Suggested Reading

Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2017;65(1):310-335.

Mandorfer M, Hernández-Gea V, García-Pagán JC, Reiberger T. Noninvasive diagnostics for portal hypertension: a comprehensive review. *Semin Liver Dis*. 2020;40(3):240-255.

Turco L, Garcia-Tsao G. Portal hypertension: pathogenesis and diagnosis. *Clin Liver Dis*. 2019;23(4):573-587.

Villanueva C, Albillos A, Genescà J, 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.