ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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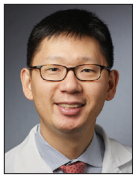
Diagnosis and Management of Portal Vein Thrombosis in Patients With Cirrhosis



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G&H Is there any need for portal vein thrombosis screening in patients with compensated cirrhosis who do not have any symptoms?

JL This is a very important question that arises commonly in clinical practice, largely because of increasing recognition that patients with cirrhosis have significantly altered coagulation status with rebalancing of both procoagulant and anticoagulant forces that can be further precipitated by clinical events such as anemia, kidney injury, infection, or medications. Because this hemostatic balance is tipped toward hypercoagulability, venous thromboembolism and portal vein thrombosis (PVT) are twice as common among patients with cirrhosis vs those without cirrhosis. PVT occurs in up to 10% to 25% of patients with cirrhosis and an estimated 20% to 40% of patients with hepatocellular carcinoma (HCC). Per current guidance of the American Association for the Study of Liver Diseases (AASLD) and the American Gastroenterological Association (AGA), routine screening for PVT is not recommended for patients with compensated cirrhosis in the absence of symptoms. However, testing should be considered among individuals who have acute symptoms, such as new-onset abdominal pain, or worsening portal hypertension (eg, new-onset variceal bleeding). It is important to make a distinction for patients who have decompensated cirrhosis who are undergoing liver transplant evaluation, for whom routine screening for PVT with Doppler ultrasound or cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is appropriate.

G&H When PVT is suspected, what imaging analysis and workup should be performed?

JL The standard of care is to pursue cross-sectional imaging with a contrast-enhanced liver protocol CT scan or MRI. The purpose of cross-sectional imaging is severalfold. First, the imaging should confirm the presence or absence of PVT. Second, it should determine the location of involvement, whether the thrombus affects the intrahepatic portal vein branches vs main portal vein vs mesenteric/splenic veins. Third, it should determine the degree of occlusion: minimal (<50% blockage), partial (>50%), or complete (100%). Furthermore, it should be determined whether there is evidence of underlying HCC, as the distinction of bland vs malignant/tumor thrombus directly influences the approach to management.

In terms of the workup, it is important to answer a few questions that will guide the treatment decision. First, the clinician should aim to determine the timing of PVT onset, determining whether it is acute or recent (<6 months) or chronic (>6 months). Second, does the patient have acute symptoms consistent with intestinal ischemia? Third, the patient should be reviewed for potential candidacy for liver transplantation. Fourth, does the patient have a high risk of bleeding, particularly gastrointestinal bleeding such as a prior history of esophageal or gastric variceal hemorrhage? Finally, the patient should be evaluated for the presence of known thrombophilia with a prior history of thrombotic risk factors and/or prior thromboembolic event.

G&H When is observation of PVT sufficient?

JL Although many patients with PVT benefit from anticoagulation, an initial period of observation may be considered for patients with cirrhosis and PVT without intestinal ischemia and asymptomatic patients with acute or recent (<6 months) thrombosis of the intrahepatic portal vein branches or less than 50% occlusion of the main portal vein, splenic vein, or mesenteric veins. It is important for clinicians to be aware that spontaneous resolution is quite common. In the largest natural history study of PVT in cirrhotic patients, which consisted of a cohort of 1243 patients and was published in *Hepatology*, Nery and colleagues observed that spontaneous regression or resolution occurred in approximately 70% of patients over 5 years. A meta-analysis of over 14 studies reported that the pooled incidence of spontaneous PVT recanalization was seen in approximately 40% of patients. In patients who are in clinical observation, serial cross-sectional imaging should be performed every 3 months to assess for interval clot progression or regression to determine the need for intervention. Furthermore, asymptomatic patients with decompensated cirrhosis who are transplant candidates who develop new-onset PVT may reasonably consider anticoagulation. The widely cited IMPORTAL study, an individual patient data meta-analysis of 5 studies with 500 patients of whom 204 (41%) were on anticoagulation and 295 (59%) were not, demonstrated that anticoagulation reduced all-cause mortality (subdistribution hazard ratio, 0.59; 95% CI, 0.49-0.70).

G&H When should endoscopic variceal screening be performed?

JL The AASLD and AGA currently recommend that patients with cirrhosis and PVT should undergo endoscopic variceal screening if they are not yet already taking a nonselective beta-blocker (NSBB) for bleeding prophylaxis, although delays in the initiation of anticoagulation for PVT in appropriate candidates should be avoided. This recommendation has become more nuanced as the standard practice of routine endoscopic screening for varices in patients with newly diagnosed compensated or decompensated cirrhosis is transitioning to a new paradigm of noninvasive assessment for clinically significant portal hypertension (CSPH) using liver stiffness measurement (LSM) based on imaging-based elastography and serum platelet count. Per AASLD and Baveno guidelines, patients with evidence of CSPH, such as the presence of LSM greater than 20 kilopascals (kPa) and platelet count less than 150,000/μL, should be routinely treated with an NSBB such as carvedilol, with the clinical objective of reducing hepatic decompensation events rather than variceal prophylaxis alone. Conversely, patients with LSM less than 20 kPa and platelet count greater than 150,000/μL are at low risk for CSPH and do not require NSBBs or screening endoscopy. Owing to the association between PVT and worsening portal hypertension, including the risk for variceal hemorrhage, patients with new-onset PVT who are already on NSBBs may be considered for endoscopic variceal screening on an individualized basis, recognizing conflicting guidance among liver specialty organizations. Although the European Association for the Study of the Liver and Baveno VII consensus guidance panel recommend variceal prophylaxis (eg, band ligation) in patients undergoing anticoagulation, this is not suggested by AASLD guidelines.

G&H Could you discuss which cirrhotic patients with PVT should receive anticoagulation?

JL Current guidelines recommend that anticoagulation should be considered for 2 groups of patients. First, patients with cirrhosis and PVT with evidence of intestinal ischemia require urgent initiation of anticoagulation to reduce the risk of ischemic injury, ideally under the care of a multidisciplinary team of specialists with expertise in the management of PVT, including gastroenterology/hepatology, interventional radiology, hematology, and surgery. Clinical features that should raise concern for intestinal ischemia include abdominal pain disproportionate to examination findings, elevated serum lactate level, sepsis, and radiographic findings of dilated bowel loops or mesenteric fat stranding. This is an unequivocal indication for anticoagulation owing to significant mortality of up to 10% to 20% in patients who develop intestinal ischemia. The second more nuanced group for whom anticoagulation is recommended consists of patients with cirrhosis without intestinal ischemia who develop acute or recent (<6 months) PVT that is greater than 50% occlusive or involves the main portal vein or mesenteric veins. Patients with involvement of more than 1 vascular bed, those with thrombus progression, liver transplant candidates, and patients with inherited thrombophilia may experience improvement in clinical outcomes and represent priority candidates. There are 2 primary benefits of anticoagulation in this group. First, recanalization may improve portal venous flow and reduce portal hypertension–related complications. Second, recanalization preserves anatomic anastomoses, which may reduce surgical/technical challenges with liver transplantation. In addition, a subset of patients who initially underwent clinical observation will experience interval clot progression with serial cross-sectional imaging, and these individuals represent candidates for anticoagulation. Individualized assessment of potential benefit/harm of anticoagulation should be pursued, with consideration of bland vs malignant thrombus (eg,

HCC), candidacy for liver transplantation, history/risk for gastrointestinal bleeding, and the patient's capacity to adhere to anticoagulation and associated monitoring.

G&H Which patients should not receive anticoagulation?

JL Current guidelines recommend against routine anticoagulation in patients with cirrhosis and chronic (>6 months) PVT with complete occlusion and evidence of collateralization (eg, cavernous transformation), as the likelihood of recanalization is very low. However, patients with chronic PVT with partial or minimal occlusion, as well as no evidence of collateralization, may be considered for anticoagulation on an individualized basis despite a lower likelihood of recanalization, particularly for individuals awaiting liver transplantation.

G&H Is there a role for vitamin K antagonists, low molecular weight heparin, and direct oral anticoagulants?

JL Vitamin K antagonists (VKAs), low molecular weight heparin (LMWH), and direct oral anticoagulants (DOACs) all represent reasonable options for patients with cirrhosis and PVT who meet criteria for anticoagulation. The selection of which agent is appropriate for a patient is nuanced and ultimately individualized based on medical considerations (eg, Child-Pugh score) and patient preference. In general, the strongest evidence is available for VKAs and LMWH, including meta-analyses that revealed significantly higher PVT recanalization rates and lower all-cause mortality in patients receiving anticoagulation vs no treatment. The major limitations include the inconvenience of parenteral injection (LMWH) and need for serial laboratory monitoring (VKAs), which may be challenging and/or onerous in some patients, although the shorter half-life of VKAs may be advantageous in the immediate pretransplant context and in patients requiring an invasive procedure or surgery. Despite limited evidence, many clinicians have adopted DOACs as an alternative anticoagulation approach owing to their convenience, and available data suggest high rates of recanalization in patients with cirrhosis and PVT. As such, DOACs represent an appropriate anticoagulation approach that may be safely administered in patients with Child-Pugh A cirrhosis and with caution in patients with Child-Pugh B cirrhosis. The use of DOACs is not presently advised in patients with Child-Pugh C cirrhosis or patients with end-stage renal disease (creatine clearance <30 mL/min).

G&H How should patients be managed if they do not respond to anticoagulation?

JL Patients with cirrhosis and PVT generally should undergo serial monitoring with cross-sectional imaging every 3 months to assess response to treatment. In patients who experience interval thrombus regression or resolution, anticoagulation is generally continued long term until the time of liver transplantation. In nontransplant candidates, anticoagulation is continued until there is radiographic evidence for complete resolution of the clot, but may be continued following resolution on an individualized basis. In patients in whom adherence is confirmed, and who do not respond to anticoagulation (no recanalization or PVT progression), consideration may be given for either treatment discontinuation or salvage intravascular procedures. Portal vein revascularization with transjugular intrahepatic portosystemic shunt (PVR-TIPS) has emerged as an increasingly attractive option for patients who have independent indications for TIPS, such as those with refractory ascites, hepatic hydrothorax, or variceal bleeding; liver transplant candidates who may benefit from recanalization to improve the technical feasibility of transplant surgery; and patients who have contraindications to or have not responded to anticoagulation. In a meta-analysis of 18 studies, PVR-TIPS was demonstrated to be effective in achieving recanalization in 80% to 90% of patients, including those with cavernous transformation or prior anticoagulation failure.

G&H Why should management differ between a cirrhotic patient with PVT being considered for liver transplantation vs someone who is not eligible for the procedure?

JL The relevance of transplant eligibility in the decision-making process for patients with cirrhosis and PVT stems from data suggesting that PVT at the time of transplant is associated with poorer patient and graft survival, largely driven by surgical/technical challenges with portal vein reconstruction and increased graft ischemic times in the perioperative setting. Fortunately, challenges with portal vein reconstruction during transplant surgery can be overcome with novel technical approaches, including physiologic end-to-end anastomoses, which have been demonstrated to be associated with similar survival as that of patients without PVT at the time of transplant.

G&H What are the biggest questions that remain in this area?

JL This is an area of clinical investigation in which adequately powered, prospective, randomized controlled trials are challenging to perform and have been rarely conducted. Therefore, clinical practice guidelines have largely been informed by evidence from retrospective

observational cohort studies. As such, there is a need for carefully designed prospective observational studies and randomized controlled clinical trials to more precisely determine the efficacy and safety of anticoagulation strategies and/or vascular revascularization procedures (overall and in specific patient subpopulations such as risk categories [eg, Child-Pugh A vs B vs C]), as well as to more clearly inform the appropriate roles of DOACs and PVR-TIPS.

Disclosures

Dr Lim reports research contracts (to Yale University) from Akero, Becton Dickinson, Gilead, Inventiva, Novo Nordisk, and Viking.

Suggested Reading

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