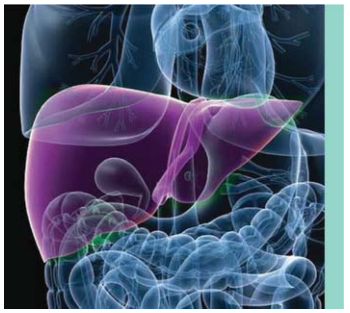

Evaluation and Management of Acute and Chronic Portal Vein Thrombosis in Patients With Cirrhosis

Kellie Young, M.D., and Robert Wong, M.D., M.S.* †

Portal vein (PV) thrombosis (PVT) is commonly seen in patients with cirrhosis and may be incidentally diagnosed in asymptomatic patients during routine imaging. Development of PVTs in this patient population is thought secondary to the low-flow states within the PV (<15 cm/second) and the hypercoagulable state induced by cirrhosis leading to increased levels of factor VIII and von Willebrand factor, as well as decreased levels of protein C, protein S, and anti-thrombin 3.[1-3] Acute PVT is associated with abdominal pain and intestinal ischemia, especially if the thrombus extends into the superior mesenteric vein (SMV).[2,3] Chronic PVT is marked by the formation of venous collaterals that bypass the occlusion[2,3] and is associated with increased risk for decompensation (ascites, variceal bleeding), as well as portal cholangiopathy.[3,4] In patients with cirrhosis, chronic PVT was previously considered a contraindication for liver transplantation until techniques were developed to allow anastomosis between the graft and patient. However, despite these advancements, occlusive PVT is still associated with higher posttransplant mortality and often leads to patient disqualification for transplantation.[4]

EVALUATION

Abdominal ultrasound with Doppler evaluation of the hepatic vasculature is part of the workup for patients with newly diagnosed liver dysfunction and is usually sufficient in detecting absent or decreased flow in the PV.[5] Although ultrasound can assess the trunk of the PV and intrahepatic branches, cross-sectional imaging (magnetic resonance imaging/computed tomography) can better

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; HR, hazard ratio; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MTHFR, methylenetetrahydrofolate reductase; PV, portal vein; PVT, portal vein thrombosis; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt; VKA, vitamin K antagonist.

From the *Department of Medicine, Santa Clara Valley Medical Center, San Jose, CA, and †Department of Gastroenterology and Hepatology, Alameda Health System–Highland Hospital, Oakland, CA.

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TABLE 1. PORTAL VEIN THROMBOSIS GRADING SYSTEM

Grade 1	<50% PV thrombosed with or without minimal extension into SMV
Grade 2	>50% PV thrombosed with or without minimal extension into SMV
Grade 3	Complete thrombosis of PV and proximal SMV
Grade 4	Complete thrombosis of PV, proximal SMV, distal SMV

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assess the potential extension of thrombi into the SMV and inferior vena cava, and thus is a more sensitive technique in evaluating thrombus severity in cases of high clinical suspicion.[2,5]

Patients with PVT are classified based on a system first put forward by Yerdel et al.[6] (Table 1). This grading system is widely used for surgical planning and predicting potential intraoperative complications.

An underlying coagulation disorder such as factor V Leiden, methylenetetrahydrofolate reductase (MTHFR), and prothrombin gene mutations have also been found to be more common in patients with cirrhosis and PVT compared with those without PVT.[3,5,7] Table 2 lists the risk factors that have been associated with thrombus development in the portal venous system. Recent European Association for the Study of the Liver guidelines[8] recommend testing for prothrombotic conditions because it can guide clinicians in determining medical therapy duration. An upper endoscopy is also indicated to diagnose and band esophageal varices or start patients on nonselective beta-blocker therapy prior to PVT treatment.

MEDICAL THERAPY

Studies of anticoagulation for acute PVT in patients with cirrhosis are limited, because most studies do not distinguish acute or chronic PVT in this patient population, and acute PVT studies are usually limited to noncirrhotic study populations. In a prospective study of 95 patients without cirrhosis but with acute PVT, anticoagulation with vitamin K antagonists (VKAs) or low-molecular-weight heparin (LMWH) led to recanalization of the portal (39%), splenic (80%), and SMVs (73%) after a median of 234 days. Ascites (hazard ratio [HR] 3.8, 95% confidence interval [CI]: 1.3-11.1) and occluded splenic vein (HR 3.5, 95% CI: 1.4-8.9) were significantly associated with failure to recanalize the PV in multivariate analysis. Two patients experienced mesenteric infarction after anticoagulation initiation and underwent intestinal resection, and nine patients had bleeding complications, although no episodes led to death.[7]

A retrospective study in Italy that focused on patients with cirrhosis with acute and subacute PVT or progressed PVT, without cavernomatous transformations, reported that anticoagulation led to partial and complete recanalization in 60% of patients. Early anticoagulation initiation ($\leq$14 days of PVT diagnosis) was significantly associated with recanalization compared with a delay in anticoagulation ($P = 0.044$). Platelet count $< 50 \times 10^9$/L had a

TABLE 2. PROTHROMBOTIC PREDISPOSITION FOR PORTAL VEIN THROMBOSIS

Condition	Diagnostic Features
Myeloproliferative disease	V617F JAK2 mutation Dystrophic megakaryocytes at bone marrow biopsy
Paroxysmal nocturnal hemoglobinuria	CD55 and CD59 deficiency in flow cytometry of peripheral blood cells Ham-Dacie and sucrose tests
Antiphospholipid syndrome	Idiopathic venous or arterial thrombosis, repeated miscarriage with high anticardiolipin antibodies *or* lupus anticoagulant *or* anti-beta2 glycoprotein 1
Factor V Leiden	Increased protein C resistance Factor V mutation: R605Q
Factor II gene mutation	G20210A mutation
Inherited antithrombin deficiency	Decreased antithrombin level *and* normal prothrombin level
Inherited protein C deficiency	Decreased protein C level *and* normal prothrombin levels
Inherited protein S deficiency	Decreased protein S level *and* normal prothrombin levels
Hyperhomocysteinemia	Increased serum homocysteine level MTHFR mutation

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significant association with anticoagulation-related bleeding complication ($P = 0.018$), but type of anticoagulation (VKA versus LMWH), duration of anticoagulation, Child-Pugh score, and international normalized ratio (INR) were not significantly associated.[9]

Although spontaneous PVT recanalization in patients with cirrhosis has been reported, the majority of these cases were for partial, nonocclusive PVTs.[10] Because there are no identified factors to predict spontaneous recanalization versus thrombus progression, treatment is recommended for both acute and chronic PVT, although caveats are made for patients with asymptomatic chronic PVT. Furthermore, prior to anticoagulation initiation, providers must weigh the benefits of therapy against bleeding risk (e.g., untreated or high-risk varices, severe thrombocytopenia $<50{,}000/mm^3$, history of life-threatening bleed) and likelihood of adherence and follow-up (in particular for VKA monitoring).

LMWH and VKA anticoagulation therapies are the most studied anticoagulation therapies in patients with cirrhosis. No significant differences in recanalization were noted between LMWH and VKA in reviews[3,10] or specific studies mentioned earlier.[7,9] Target INR during VKA therapy is 2 to 3, which may pose difficulties with monitoring if the patient's baseline INR is already elevated due to hepatic synthetic dysfunction.[1] LMWH offers a benefit of being a stable weight-based dose and no laboratory monitoring is required; however, patient compliance with daily injections may be a barrier to consistent dosing. Impaired renal function (creatinine clearance [CrCL] < 30 mL/min) is also a barrier to LMWH therapy. In a randomized, prospective study of patients with hepatitis B cirrhosis and PVT (both acute and chronic) treated with either 1 mg/kg LMWH twice a day or 1.5 mg/kg LMWH daily, investigators found no significant difference in rate of complete ($P = 0.224$) or partial ($P = 0.129$) recanalization at 6 months.[11] However, investigators did observe higher bleeding complications (epistaxis, hematuria) in patients in the 1.5 mg/kg daily LMWH treatment arm compared with the 1 mg/kg LMWH twice-daily treatment arm.

Novel oral anticoagulants are not well studied in patients with cirrhosis, but they are desirable due to the ability to avoid both injections and laboratory monitoring. Although not formally recommended, case reports have been published that document success in recanalization with rivaroxaban.[12]

Experts recommend at least 6 months of anticoagulation therapy in acute PVT, and longer if patients have evidence of mesenteric thrombus extension or an underlying prothrombotic condition.[7] Anticoagulation in patients with cirrhosis and PVT is an individualized decision for each patient, but it is generally recommended if patients are symptomatic or have progression of their liver disease. Duration of therapy is also not well defined and may extend to time of transplant if patients are candidates. Goals of anticoagulation therapy are for PV recanalization or prevention of thrombus occlusion, and thus preventing or delaying portal hypertension complications. For liver transplant candidates, recanalization of the PV tree is also desirable to avoid intraoperative complications and posttransplant mortality associated with graft anastomosis or perivenous inflammatory changes.

INTERVENTIONAL THERAPY

Transjugular intrahepatic portosystemic shunt (TIPS) addresses the decreased portal flow rate and can also be considered for treatment of PVT. In a single-center, retrospective study, 70 patients with cirrhosis and PVT underwent TIPS without anticoagulation or local thrombolysis, with 57% of patients achieving complete recanalization and 30% with partial recanalization at 2 years postprocedure.[13] Five percent of patients (n = 2) who initially had complete recanalization had rethrombosis. Predictors of

TABLE 3. MEDICAL AND INTERVENTIONAL THERAPIES FOR ACUTE AND CHRONIC PORTAL VEIN THROMBOSIS

	PVT	
	Acute	Chronic
Medical therapies	Anticoagulation: LMWH, VKA	Anticoagulation: LMWH, VKA
	Antibiotics (if evidence of phlebitis)	
Interventional therapies	TIPS	TIPS
	Transjugular/transhepatic thrombolysis	
	Surgical thrombectomy	

complete recanalization in multivariate analyses were single vein involvement (HR 2.45, 95% CI: 1.17-5.14) and lack of gastric/esophageal varices (HR 14.99, 95% CI: 2.81-79.81).[13]

Treatment with TIPS and anticoagulation is also possible in both acute and chronic PVT. Senzolo et al.[14] reported using TIPS prior to anticoagulation initiation in patients with high-risk varices (n = 2), as well as after anticoagulation in patients who had progression of thrombus with resulting complications of portal hypertension (n = 5). In patients who had TIPS placed prior to anticoagulation, the thrombus stabilized or disappeared completely. In the group who had TIPS placed after their thrombus progressed despite anticoagulation, one patient had complete recanalization, three had stabilization of their thrombus, and one died of intestinal infarct.[14]

Transhepatic and transjugular directed thrombolysis are also described as approaches for acute PVT in case reports. Although studies report comparable recanalization rates as anticoagulation, there have been reported higher risks for bleeding and mortality.[8] A retrospective study of 20 patients with symptomatic acute or subacute PVT and/or mesenteric vein thrombosis with no response to anticoagulation evaluated survival and recanalization rates with treatment of catheter-directed thrombolytics.[15] Fifteen patients in this study achieved complete (n = 3) or partial (n = 12) recanalization; however, 60% (n = 12) of patients experienced major complications, including bleeding requiring transfusions and death from gastrointestinal hemorrhage.[15]

Surgical thrombectomy has also been utilized in select patients who present with acute abdomens suggestive of bowel ischemia and are also undergoing exploratory laparotomy for bowel resection.[16]

CONCLUSIONS

PVT in the setting of cirrhosis poses increased risk for intestinal ischemia in acute cases, as well as hepatic decompensation, increased difficulty with liver transplant surgery, and higher posttransplant mortality for chronic PVT. Treatment in both the acute and chronic stages of PVT with either anticoagulation, TIPS, or antithrombolytic therapy have been shown to improve recanalization rates (Table 3); however, the decision to treat PVT is complex, and clinicians must first consider multiple patient factors (i.e., bleeding risk, complications of therapy, disease progression, symptoms, and likelihood of transplantation).

CORRESPONDENCE

Kellie Young MD, Department of Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose CA 95128. E-mail: kellie.young@hhs.sccgov.org.

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