

## **Q:** What are the management considerations for venous thromboembolic events in patients with cirrhosis?

A 61-year-old man with Child-Pugh class A cirrhosis, admitted to the hospital with community-acquired pneumonia, is diagnosed with left lower-extremity proximal deep vein thrombosis (DVT) with no evidence of impaired venous drainage. Admission laboratory values include:

- Hemoglobin 10 g/dL (reference range 13.8–17.2 g/dL)
- Platelet count  $60 \times 10^9/L$  ( $150\text{--}400 \times 10^9/L$ )
- Creatinine 1.0 mg/dL (0.7–1.3 mg/dL)
- International normalized ratio (INR) 1.8 (0.8–1.1).

What is the appropriate management of his DVT?

**A:** This patient's treatment should start with a direct oral anticoagulant (DOAC) or low-molecular-weight heparin (LMWH).<sup>1</sup> His history suggests that the DVT was provoked by immobility secondary to pneumonia. Patient preference and drug cost should further guide management, as excellent adherence is needed to prevent future complications and recurrence.

### **■ INTERPRETING LABORATORY RESULTS: A TENUOUS BALANCE**

Hemostatic laboratory abnormalities are common in patients with liver disease and can include thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time, elevated INR, and decreased fibrinogen. Patients with cirrhosis were previously thought to have an increased risk only of bleeding as opposed to an increased risk of thrombosis.<sup>1</sup> But current evidence argues for a “rebalanced”

hemostatic state from reciprocal changes in both pro- and antihemostatic pathways.<sup>2</sup> Prothrombin time, activated partial thromboplastin time, and INR are often elevated in patients with cirrhosis because of low levels of coagulation factors as well as decreased levels of protein C, protein S, and antithrombin—all synthesized by the liver.<sup>2</sup> Additional hypercoagulable changes include the imbalance of von Willebrand factor with ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), hyperactive platelets, enhanced thrombin-generating capacity, and, occasionally, hypofibrinolytic states.<sup>1</sup>

Patients with cirrhosis are therefore susceptible to bleeding and thrombotic events secondary to this tenuous balance. A systematic review and meta-analysis that included 11 studies determined there was a significantly increased risk of pulmonary embolism and DVT (odds ratio [OR] 1.7) in patients with cirrhosis compared with controls.<sup>3</sup>

### **Predicting risk of venous thromboembolic events**

Among several clinical scoring systems created to predict risk of a venous thromboembolic event (VTE), only 2 have included patients with liver disease.<sup>1,4,5</sup>

The **Padua Prediction Score** is calculated using 11 variables with associated point values.<sup>4</sup> Patients with cirrhosis whose Padua score was 4 or greater, considered high-risk, were significantly more likely to develop VTE (OR 12.7).<sup>4</sup>

The **International Medical Prevention Registry on Venous Thromboembolism (IMPROVE)** risk score was developed using data from 15,156 patients and

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included those with a history of hepatic failure.<sup>5</sup> The IMPROVE score is calculated using 7 variables with associated point values. Patients with an IMPROVE score greater than 2 may benefit from thromboprophylaxis. In patients whose score was greater than 4, approximately 5.7% developed VTE within 3 months.<sup>5</sup>

Each scoring system has limitations. Neither was prospectively validated specifically for patients with cirrhosis, although the IMPROVE model included 235 patients with prior hepatic failure.<sup>5</sup>

### ■ VTE PROPHYLAXIS: EVIDENCE IS LIMITED

Risk of VTE in patients with cirrhosis increases with prolonged hospitalization, immobilization, surgery, and male sex. Because of perceived increased bleeding risk in patients with cirrhosis, VTE prophylaxis has not been used routinely in this population, and evidence supporting it is limited. No randomized controlled trial has compared outcomes of VTE prophylaxis in patients with cirrhosis.<sup>1,6</sup> A large meta-analysis found that patients with cirrhosis have a 1.9% higher absolute risk of VTE than patients without cirrhosis.<sup>3</sup> The American Gastroenterological Association therefore recommends standard anticoagulation prophylaxis in hospitalized patients with cirrhosis as a conditional recommendation with very low certainty of evidence.<sup>6</sup> The European Association for the Study of the Liver (EASL) recommends that patients with cirrhosis who are at risk of VTE receive LMWH, noting that the strategy has unclear efficacy but a reasonable safety profile.<sup>1</sup>

DOACs are not currently approved by the US Food and Drug Administration (FDA) for VTE prophylaxis in hospitalized patients, and data are lacking to support their use in hospitalized patients with cirrhosis. Current American Society of Hematology guidelines recommend LMWH rather than unfractionated heparin (UFH) because LMWH requires less frequent administration.<sup>7</sup> Clinical judgment and VTE risk assessments may further aid clinicians. A meta-analysis that included more than 5,000 patients lacked sufficient evidence to advise for or against VTE prophylaxis in patients with cirrhosis, although its use was not associated with significant bleeding risk.<sup>8</sup>

### ■ TREATMENT: THE RISK-BENEFIT RATIO AND PATIENT ADHERENCE

Despite limited evidence for anticoagulation in patients with cirrhosis, VTE should be treated in the absence of absolute contraindications. Each patient must be

considered carefully to ensure that benefits outweigh risks, as most studies excluded patients with active or recent bleeding. Duration of anticoagulant therapy is guided by whether the event is provoked or unprovoked, among other considerations. Patient adherence is critical for successful treatment and prevention of future complications.

### Traditional anticoagulants

The EASL issued a weak recommendation for the use of vitamin K antagonists or LMWH in patients with Child-Pugh class A cirrhosis: LMWH is favored in patients with Child-Pugh class B and C cirrhosis, and UFH is recommended in the presence of renal impairment.<sup>1</sup>

**Vitamin K antagonists** are not ideal. They require frequent monitoring, have a narrow therapeutic range, and have many drug-drug interactions.<sup>1</sup> They are particularly challenging in patients with cirrhosis, whose altered INR baselines make it difficult to establish a therapeutic range. The relatively higher incidence of INR variability between laboratories in this patient population is also problematic. Vitamin K antagonists should be avoided in patients with cirrhosis who have a prolonged baseline prothrombin time and INR.<sup>1,9</sup>

The anticoagulant effect of LMWH has yet to be fully characterized in patients with cirrhosis, and traditional monitoring with anti-Xa assays may be unreliable.<sup>1</sup> Large randomized controlled studies comparing traditional anticoagulants are lacking in treating DVT and pulmonary embolism in patients with cirrhosis, but multiple studies have evaluated these agents in the treatment of portal vein thrombosis in this population and have suggested reasonable safety and efficacy of UFH and LMWH.<sup>1</sup>

The EASL guidelines strongly recommend use of DOACs in patients with Child-Pugh class A cirrhosis and cautious use in patients with Child-Pugh class B disease. The FDA recommends avoidance of oral Xa inhibitors in patients with Child-Pugh class B or C cirrhosis, but supports dabigatran for patients with Child-Pugh class A and B disease.<sup>1</sup>

Overall, more prospective investigation of DOAC safety and efficacy in this patient population is needed. Most evidence to date is based on case series, retrospective studies, and small observational studies. Retrospective data with DOACs in patients with cirrhosis and a variety of indications have shown safety and bleeding events comparable to those with traditional anticoagulants such as vitamin K antagonists, LMWH, and UFH.<sup>1</sup> In the context of portal vein thrombosis, edoxaban when compared with warfarin had a higher

proportion of patients with complete resolution of portal vein thrombosis, with less thrombosis progression and a similar rate of bleeding events.<sup>10</sup>

## THE CLINICAL BOTTOM LINE

Patients with cirrhosis exhibit a rebalanced hemostatic state that makes them prone to VTE. The choice of

anticoagulation for prophylaxis and treatment should be individualized, and prospective studies are needed to refine the decision-making progress.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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