Hematological Issues in Liver Disease

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KEYWORDS

• Cirrhosis • Acute liver failure • Thrombocytopenia • Coagulopathy • Thrombosis • Anticoagulation

KEY POINTS

- The international normalized ratio (INR) should not be used as a measure of coagulation status in patients with liver failure.
- Liver failure results in a state of "rebalanced hemostasis" marked by a decrease in both procoagulation and anticoagulation factors.
- Patients with liver disease are not auto anticoagulated.
- Hospitalized patients with liver disease have high thrombotic risk and should receive pharmacologic antithrombotic prophylaxis in the absence of contraindications.
- Patients with liver disease undergoing invasive procedures should have appropriate platelet counts for the proposed procedure. The best approach to manage elevations in INR is unclear.

INTRODUCTION

Hepatic dysfunction results in complex hematologic abnormalities; the pathophysiological basis of these abnormalities are frequently misunderstood and may lead to suboptimal management. Diagnostic criteria for liver failure include elevation in the international normalized ratio (INR). Using elevations in conventional assays for anticoagulation monitoring has resulted in the assumption that liver disease, both acute and chronic, is a state of hypocoagulability, marked by a predilection for bleeding diatheses. Recent investigations into the coagulation milieu have elucidated that many patients with underlying acute or chronic liver dysfunction do not have evidence of auto-anticoagulation.[1] Counterintuitively, patients actually have disorders of the coagulation system that result in normal coagulation, or sometimes even a hypercoagulable

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state that can clinically manifest with thrombotic complications. Bleeding diathesis that occur in patients hospitalized with acute liver failure (ALF) and cirrhosis are more likely attributable to the hemodynamic consequences of liver disease, such as increased portal and splanchnic pressures. In recent years, it has become evident that appropriately assessing patients for the risk of bleeding and thrombosis cannot be done with traditional measures of coagulation, such as prothrombin time (PT), partial thromboplastin time (PTT), or INR. In this context, there is now an emerging role for viscoelastic testing to determine the risk of bleeding and guide blood product replacement therapy in patients with liver disease. Further, prophylaxis against thrombosis, treatment of thrombosis, and transfusion of blood products to treat bleeding requires knowledge of the alterations of the hematologic system specific to patients with liver disease. In this article, we discuss mechanisms for the coagulation abnormalities, comment on the limitations of laboratory testing, and review clinical manifestations of hematological alterations in patients with acute and/or chronic liver disease.

MECHANISMS OF HEMATOLOGIC ABNORMALITIES IN LIVER FAILURE

There has been considerable refinement in the understanding of the coagulation changes occurring in liver failure in the past 10 years. A disease traditionally thought to result in an anticoagulated state that places patients at increased risk of bleeding has now been recategorized. "Rebalanced hemostasis" is the term that has been used to describe the coagulation abnormalities specific to liver disease, wherein there is a commensurate fall in coagulation proteins that counterbalance the decrease in the factors that promote coagulation.[1] This balance is tenuous, as patients with liver disease can present with complications of both bleeding and thrombosis. Although there are differences between the hematologic abnormalities in ALF and chronic liver disease with cirrhosis, both manifest adaptations for achieving a rebalanced state (**Table 1**). A new balance is reached with procoagulation factors, anticoagulant factors, platelets, von Willebrand factor (vWF), and fibrinolysis.

Coagulation Factors

The liver is responsible for synthesizing most of the proteins that control the coagulation system. This includes procoagulant factors (F) I (fibrinogen), II (prothrombin), V, VII, IX, X, XI, XII, XIIIa, and also includes the anticoagulants protein C, protein S, and antithrombin. In hepatic dysfunction, levels of these factors are decreased, but

Table 1
Rebalanced hemostasis in acute liver failure compared with cirrhosis

	Acute Liver Failure	Cirrhosis
Anticoagulants		
Protein C/S	↓	↓
Antithrombin	↓	↓
Procoagulants		
Coagulation factors	↓↓	↓
Factor VIII	↑	↑
Fibrinogen	↓	↓↓
Platelets	↓	↓
Von Willebrand Factor	↑	↑

Abbreviations: ↑, protein factors are up-regulated in disease; ↓, protein factors are down-regulated in disease; Protein C/S, protein C/protein S.