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REVIEW ARTICLE

Algorithms for managing coagulation disorders in liver disease

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Abstract

Patients with advanced liver disease have traditionally been considered at risk for bleeding complications. However, although bleeding in patients with cirrhosis frequently occurs due to complications of portal hypertension, research performed within the last 15 years has increasingly shown that hemostasis in patients with liver failure generally achieves a state of "rebalance", whereby compensatory systems restore a relatively neutral or even slightly pro-thrombotic state. Much recent clinical and in vitro research has, in fact, shown over-compensation, such that patients with acute and stable chronic liver failure may have a thrombotic tendency, which may participate in the progression of liver disease and cause systemic and portal thrombosis. Investigators have started to identify differences in hemostasis in patients with unstable cirrhosis, the newly defined syndrome of acute-on-chronic liver failure (ACLF), compared to those with stable cirrhosis. The following discussion will summarize much of the background of rebalanced hemostasis in patients with cirrhosis and acute liver failure (ALF), and suggest management algorithms for coagulation abnormalities before invasive procedures, during active bleeding, and for prophylaxis and treatment of thrombotic complications.

Keywords Hemostasis · Cirrhosis · Acute liver failure · Bleeding · Thrombosis · Coagulopathy

Abbreviations

ACLF	Acute-on-chronic liver failure
ADAMTS-13	A disintegrin and metalloprotease with thrombospondin type-1 motifs 13
ALF	Acute liver failure
AT	Antithrombin
HCC	Hepatocellular carcinoma
ICP	Intracranial pressure
INR	International normalized ratio of the prothrombin time
LMWH	Low-molecular-weight heparin
MOSF	Multiorgan system failure
PVT	Portal vein thrombosis
RBC	Red blood cells
rFVIIa	Recombinant-activated factor VII
ROTEM	Rotational thromboelastometry
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
TEG	Thromboelastography
TF	Tissue factor
TM	Thrombomodulin
VTE	Venous thromboembolism
vWF	VonWillebrand factor

Introduction

Patients with acute or chronic liver disease have been historically treated as having a bleeding diathesis based on the standard laboratories suggesting insufficient hemostasis [low platelet count and high international normalized ratio (INR) of the prothrombin time]. The perception is also based upon the frequent incidence of portal hypertensive bleeding in patients with cirrhosis. However, clinically significant bleeding complications apart from gastrointestinal bleeding are relatively uncommon in advanced liver disease [1]. Factors which fuel the perception of a bleeding diathesis differ according to the acuity and stability of liver disease (Table 1). In patients with stable cirrhosis, thrombocytopenia is often moderately

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Table 1 Clinical features of cirrhosis, ACLF, and ALF contributing to the perception of bleeding risk

Feature	Stable cirrhosis	Acute liver failure	Unstable cirrhosis (ACLF)
Portal hypertension	+++	−/+	+++
Synthetic failure/↑ INR	+	+++	+++
Thrombocytopenia	++	+	+++
Systemic inflammation	+	+++	+++

The relative severity of the indicated clinical feature of cirrhosis, ACLF, and ALF is depicted as: +++ major feature; +/++ mild–moderate feature; −/+ insignificant feature

severe due to platelet sequestration within the spleen, but the degree of INR elevation is relatively modest. In contrast, patients with ALF usually exhibit dramatically elevated INR and more moderate thrombocytopenia. The newly defined syndrome of acute-on-chronic liver failure (ACLF), in which patients with cirrhosis acutely decompensate and progress to multi-organ system failure (MOSF) [2], shares the severe features of both stable cirrhosis and ALF, and is characterized by marked thrombocytopenia and elevated INR. In all three clinical syndromes, the varying severity of the systemic inflammatory response syndrome (SIRS) compounds the clinical impression of unstable hemostasis, but actually may signify activation of endothelial compensatory mechanisms.

A major reason for overstating bleeding risk in patients with liver disease has been the reliance on the INR as a marker of bleeding risk [3]. However, the INR was designed to measure the effects of warfarin administration rather than predicted bleeding risk; indeed, there is no correlation between the INR and post-procedural bleeding in patients with liver disease [4]. Simplistically, the INR assay measures only a limited portion of hemostasis (Fig. 1), and does not account for the intrinsic coagulation cascade, activated platelets, or pathways which inhibit thrombin formation.

Increasing evidence has been presented over the last 10–15 years, documenting that patients with acute and stable chronic liver disease maintain a state of "rebalanced hemostasis" or even hypercoagulability [5, 6]. The following discussion will explore the data which redefine the magnitude of the bleeding diathesis in patients with stable cirrhosis, ALF, and ACLF, which are presented in Supplemental Figures and Tables. Mechanisms of rebalance, and important exceptions to the "rule" of rebalance, will be highlighted. Finally, management algorithms for hemostatic abnormalities in patients with advanced liver disease will be presented with a rationale and citations, when available, recognizing that rigorous clinical studies to document safety and efficacy of these recommendations have yet to be performed.

The state of hemostasis in patients with acute and chronic liver disease

Stable cirrhosis is generally a state of rebalanced hemostasis

Exclusive of the risk of portal hypertensive gastrointestinal bleeding, a persuasive argument can be made on clinical grounds that patients with advanced but stable cirrhosis may not have a bleeding diathesis [1]. In contrast to patients with hereditary or acquired coagulation factor deficiencies, patients with stable cirrhosis do not present with clinically significant, spontaneous bleeding, such as hemarthroses. The lack of efficacy of recombinant activated factor VII (rFVIIa) to treat or prevent esophageal variceal bleeding/rebleeding strongly argues against abnormal hemostasis as a cause of variceal bleeding [7, 8]. Finally, liver transplantation in recent times can often be performed without appreciable blood loss or the need for blood product transfusions.

The seminal explanation for the apparent paradox of high INR and low platelets yet low incidence of non-portal hypertensive bleeding was proposed by Tripodi and associates in 2005 [9]. These investigators recognized deficiencies of the thrombin generation assay; in that, the test lacks thrombomodulin (TM), an endothelial activator of protein C, the key anticoagulant protein in plasma. As shown in Suppl Fig. 1, patients with cirrhosis were found to have lower thrombin generation than healthy controls due to decreased synthesis of pro-coagulant factors by the ailing liver. However, the addition of TM to the reaction mixture revealed that thrombin generation in cirrhotics and healthy controls was similar, suggesting that, under more physiologic in vitro conditions in which the anticoagulant activity of protein C is fully expressed, liver failure-induced deficiencies of both pro- and anticoagulant proteins result in normal levels of thrombin generation.

Activated platelets are integral to thrombin generation, and their absence in vitro represents another deficiency of standard coagulation tests. The platelet count at which normal levels of thrombin were generated was estimated in another seminal study by Tripodi et al. [10]. In normal healthy controls, they found that the 90th percentile of

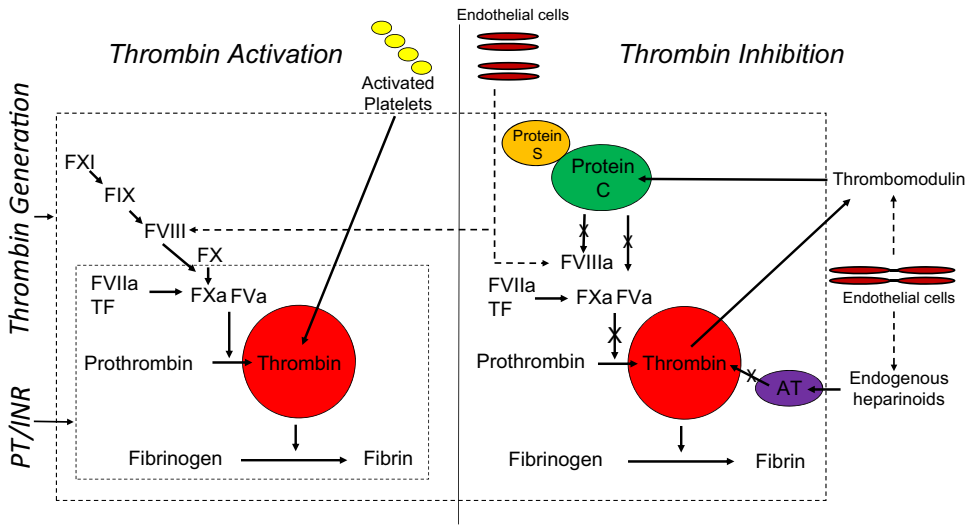


Fig. 1 Simplified representation of pathways of thrombin generation and inhibition, yielding fibrin. Thrombin is generated by the sequential activation of liver-derived pro-hemostatic factors in the traditional coagulation cascades, but also by activated platelets. Factor VIII, derived from endothelial cells, is increased in both cirrhosis and acute liver failure. Thrombin generation is limited by liver-derived anticoagulant proteins C, S, and antithrombin (AT). The protein C/S complex serves as an anticoagulant factor by inactivating factors Va and VIIIa. Endothelial cells also produce two anticoagulant factors, thrombomodulin (TM), which is required for full activation of protein C, and endogenous heparinoids, which activate AT. In the absence of TM in vitro, thrombin generation is overestimated, because protein C is not fully activated. The dotted box indicated represents the scope of the INR as a measure of hemostasis, measuring contributions only from the factor VII-tissue factor (TF) pathway, and the final common pathway of the coagulation cascades. The second larger dotted box represents the scope of the thrombin generation assay, which is more physiologic because it includes contributions from activation and inhibitory pathways, and can be methodologically modified to also account for activated platelets and TM

thrombin generation in TM-modified assays was ~ 875 nmol/l. Using this definition of normal thrombin generation, the experiments were repeated using plasma from patients with cirrhosis, and determined that a platelet count of 56×10^9/l was adequate to generate thrombin at the 90th percentile of normal. Clinical observations also appear to support this in vitro observation. As shown by Seeff and colleagues [11], bleeding complications after liver biopsies in the HALT-C Trial occurred more commonly in patients with advanced liver fibrosis from hepatitis C and platelet counts $< 60 \times 10^9$/l.

Other endothelial, pro-hemostatic proteins participate in the rebalance of hemostasis in patients with stable cirrhosis. vonWillebrand factor (vWF) serves to bind platelets to collagen in denuded endothelium and promotes platelet aggregation. As shown in Suppl Fig. 2, Lisman et al. [12] have shown that vWF levels in plasma increase as a function of the severity of liver failure, suggesting that thrombocytopenia may be rebalanced by high vWF. Deficiency of the liver-derived regulatory protein of vWF, ADAMTS-13, may also compensate, since ADAMTS-13 deficiency may result in larger vWF multimers with increased platelet–endothelial binding capacity [13]. Finally, plasma factor VIII levels are increased in patients with cirrhosis as part of the SIRS, and can partially compensate for deficient liver-derived pro-hemostatic factors [5].

Patients with stable cirrhosis also appear to be rebalanced in fibrinolytic pathways. Plasminogen deficiency due to liver failure is thereby rebalanced by deficiency in antifibrinolytic proteins α2-antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI), and by high levels of tissue plasminogen activator [1]. Thus, compensatory mechanisms establish a delicate state of stability of all phases of hemostasis (Fig. 2) as long as the clinical state of a patient with cirrhosis is unperturbed by a number of destabilizing complications (see below).

Cirrhosis is also hypercoagulable state in some patients

The problem of thrombosis has increasingly been recognized as a major clinical problem in patients with cirrhosis. Wanless et al. [14] first recognized the problem of microvascular thrombosis within the liver as a mechanism of disease progression. In a meticulous pathologic study of explanted livers, they found a direct correlation of venous microobliterative lesions and focal parenchymal extinction within the same vascular distribution. Clinical observations have also supported the concept of cirrhosis as a hypercoagulable state in macrovascular beds, including the

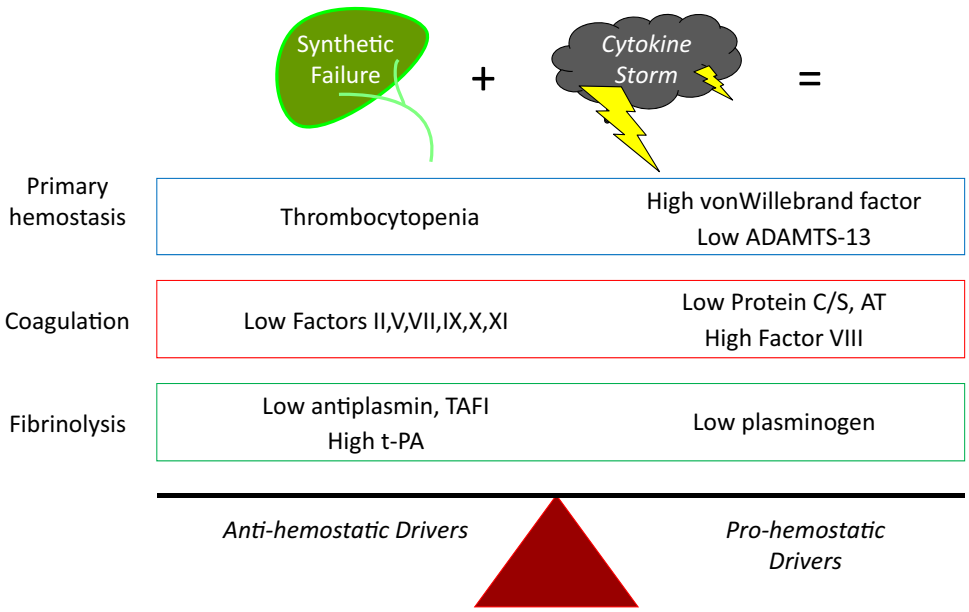


Fig. 2 Three phases of hemostasis in patients with cirrhosis and acute liver failure exist in a state of "rebalance". Primary hemostasis in both conditions is defective due to thrombocytopenia, but is compensated for by platelet microparticle formation (for ALF), and by increased vWF synthesis by endothelial cells. Deficiency of ADAMTS-13, a liver-derived protease, may also increase vWF multimer size and thus its ability to promote the adherence of platelet-to-endothelial defects. Defects in secondary hemostasis, in which liver-derived, pro-hemostatic factors are decreased because of liver failure, are compensated for by deficiencies of liver-derived, antihemostatic proteins, protein C/S and antithrombin (AT), and by high levels of endothelial cell-derived factor VIII. Finally, fibrinolysis is defective because of low liver-derived plasminogen, but compensated for by low levels of antifibrinolytic, liver-derived proteins such as α2-antiplasmin, and high levels of endothelial cell-derived tissue plasminogen activator (tPA) (adapted from Tripodi and Mannucci [1])

portal, peripheral venous, and neurovascular circulations [15–18]. A recent meta-analysis of 15 controlled studies (~ 1.5 million non-cirrhotics and 700,000 cirrhotics) showed an odds ratio of 1.7 for total VTE, 1.8 for risk of deep venous thrombosis, and 1.6 for risk of pulmonary embolism in patients with cirrhosis compared to controls (Suppl Fig. 3) [19]. Continuous renal replacement therapy (RRT) circuits in patients with liver failure also have decreased patency rates than in controls, and can be prevented by anticoagulation [20]. Thus, the notion that patients with cirrhosis are "autoanticoagulated" because of high INR and low platelets has been strongly refuted.

Hypercoagulability in patients with stable cirrhosis has been quantified by Tripodi et al. [5], noting high factor VIII levels and low protein C and AT levels in patients with cirrhosis compared to controls (Suppl Fig. 4). Ratios of pro- and anticoagulants (factor VIII/protein C and factor VIII/AT) increased in proportion to the Child–Pugh class, creating an imbalance favoring thrombosis. The imbalance of pro-and anticoagulants appears to have clinical significance, as a high factor VIII/protein C ratio was subsequently shown to promote new-onset ascites and variceal bleeding (Suppl Fig. 5) [21].

Non-malignant portal vein thrombosis (PVT) occurs in up to 25% of patients with cirrhosis awaiting liver transplantation [22], and cirrhosis is the most important risk factor [23]. Often, PVT is discovered as an incidental finding during ultrasound surveillance for hepatocellular carcinoma (HCC) [24]. The risk of PVT reflects the severity of underlying cirrhosis and its incidence increases with decompensation. Although macrovascular PVT may be responsible for the progression of cirrhosis [24], its occurrence is associated with acute decompensation, variceal bleeding, and increased mortality [25]. Carnevale et al. [26] have recently provided a possible explanation for the association of the severity of cirrhosis, decompensation, and the incidence of PVT. Endotoxin released from gut luminal bacteria into portal blood was shown to increase the release of factor VIII and vWF from cultured endothelial cells, providing a possible mechanism by which bacterial and bacterial product translocation may promote thrombosis of the portal circulation.

Since PVT can result in gut ischemia, bowel infarction, gastrointestinal bleeding, and hepatic ischemia, and render a patient un-transplantable; prevention of PVT in cirrhosis is highly desirable. A seminal study by Villa et al. [27] randomized 70 patients with stable cirrhosis to enoxaparin (4000 IU/day) or placebo for 48 weeks. The 2-year prevention of PVT detected by 3-month ultrasound exams was 0% in the enoxaparin-treated group but 27.7% in the control group ($p = 0.001$; Suppl Fig. 6). Moreover, the incidence of hepatic decompensation was lower, and

overall transplant-free survival higher, in patients who received enoxaparin independently of PVT prevention. This study strongly supports work 17 years prior by Wanless et al. (Suppl Fig. 6), who painstakingly correlated progression of parenchymal collapse in explanted livers with thrombotic occlusion of the hepatic microvasculature within the same vascular distribution [14].

Rebalanced hemostasis in patients with cirrhosis may be destabilized in patients with ACLF

The discussion above suggests that global hemostasis in patients with stable cirrhosis exists in a rebalanced equilibrium tipped toward a slightly pro-coagulant state. However, this state of rebalance is fragile, and circumstances in cirrhosis conspire to destabilize hemostasis, leading to bleeding and, in some cases, thrombosis (Table 2). For example, active gastrointestinal bleeding from portal hypertension adversely affects clot strength [28], because it further depletes pro-coagulant factors. Infection destabilizes hemostasis by inducing hemodynamic instability and elaborating endothelial substances which tip the balance toward bleeding (endogenous heparinoids) [29]. Destabilized hemostasis in patients with cirrhosis may also result in thrombosis [30]; precipitating events may include spontaneous bacterial peritonitis [26], over-judicious platelet transfusion of platelets or use of thrombopoietin agonists, or platelet activation and generation of pro-coagulant microparticles (MPs) by infection, endotoxemia, or the development of hepatocellular carcinoma (HCC) [31, 32]. ACLF ensues after many of these inciting events, and "coagulation failure" is one of the defining features of ACLF [2] (Suppl Fig. 7).

Much less information exists regarding the nature and extent of abnormal hemostasis in ACLF than in stable cirrhosis. In the first such study, Fisher et al. [33] showed exaggerated hemostatic abnormalities in ACLF as compared to patients with stable cirrhosis, and generally intermediate abnormalities between the extremes in patients with acutely decompensated cirrhosis without extra-hepatic organ failure (Suppl Table 1). Thus, patients with ACLF were shown to have higher INR, vWF, and factor VIII levels, and lower fibrinogen and ADAMTS-13 levels, than patients with stable cirrhosis. Moreover, thrombin generation in patients with ACLF was similar to patients with stable cirrhosis in the presence of TM, suggesting that these exaggerated abnormalities also tend to be rebalanced. However, using rotational thromboelastometry (ROTEM), a hemostatic assay of whole blood, Blasi et al. [34], have recently shown that a hypocoagulable state exists commonly in patients with ACLF (61%), more so than in patients with acutely decompensated cirrhosis without organ failure (29%), and hypocoagulability predicts 28-day mortality (45 vs. 16% in patients with normal ROTEM parameters; $p = 0.025$). Interestingly, hypocoagulable ROTEM results did not predict bleeding complications or the need for transfusions, suggesting that non-bleeding events were more commonly the reasons for death.

Whether precipitated by a bleeding or non-bleeding event, patients with ACLF admitted to the intensive care unit (ICU) are well known to be at increased risk of bleeding complications. In a study of 211 patients with cirrhosis admitted to the ICU, 87% of whom had ACLF, Drolz et al. [35] found 35 patients prospectively developed new major bleeding events. The most highly predictive of new major bleeding events was the plasma fibrinogen concentration, followed by platelet count, and partial thromboplastin time (aPTT); importantly, the INR was not predictive (Suppl Table 2). In multivariate analyses, independent predictors of major bleeding included bleeding on admission to the ICU, a fibrinogen of < 60 mg/dl, platelet count $< 30 \times 10^9$/l, and aPTT > 100 s. These data imply potentially important guidelines with which to manage hemostatic abnormalities in patients with ACLF.

Bleeding risk in patients with ALF

The dramatic elevation of INR in patients with ALF not only defines the syndrome, but also promotes great anxiety

Table 2 Destabilizing influences on rebalanced hemostasis in patients with cirrhosis and ALF

Hemodynamic instability
Active bleeding: exacerbates deficiency of pro-coagulant factors with short half-life
Infection: releases endogenous heparinoids
Gut-derived endotoxin: vWF and FVIII-induced thrombosis
Endothelial dysfunction (SIRS)
Microparticles (pro-thrombotic)
Renal failure
Qualitative platelet dysfunction

on the part of clinicians. The trend in INR is an invaluable indicator of outcome in ALF [36], but not because it predicts bleeding complications. In fact, bleeding complications in patients with ALF occurred in only ~ 10% of patients enrolled in the ALF Study Group Registry [37]. Nearly 84% of these bleeding episodes were from an upper gastrointestinal source, and were clinically insignificant, neither requiring transfusion nor endoscopy, and only 1.8% were the proximate cause of death. Intracranial bleeding was rare (10%), only half were due to intracranial pressure (ICP) monitor placement; the other half were spontaneous and presumably related to intracranial hypertension. However, intracranial bleeding due to ICP monitor placement carried a 50% mortality. Thus, the magnitude of bleeding complications pales in comparison to the unease with which clinicians often approach patients with ALF in managing their hemostatic abnormalities.

Although patients with ALF develop thrombocytopenia, the nadir platelet count is usually not as low as patients with ACLF [38]. The primary mechanism of declining platelet counts in ALF differs from those in cirrhosis, since portal hypertension and hypersplenism are milder in the former [39]. Instead, platelet activation by the intense SIRS [40] probably leads to platelet clearance [38]. The activation of platelets is accompanied by production of highly pro-thrombotic platelet-derived microparticles, which also may participate in a relative hypercoagulable state [41].

Although the widespread use of blood product transfusion as prophylaxis against bleeding might explain the low incidence of bleeding complications after admission to the hospital for ALF, historical data from the ALF Study Group Registry refute this possibility. As shown in Supple Fig. 8, blood product transfusion has declined steadily and dramatically in the US over the 18 years of the Registry, while bleeding complications have remained stable at approximately 10% per year [37].

ALF is often a state of rebalanced hemostasis

The conundrum of a perceived bleeding tendency in the face of infrequent bleeding complications strongly suggests that ALF, similar to stable cirrhosis, represents a state of rebalanced hemostasis. As shown in Table 3, hemostasis assessed by thromboelastography (TEG), a viscoelastic assay of clot formation, is usually normal [42]. High factor VIII and vWF levels likely participate in compensation for low pro-coagulant factors and thrombocytopenia, as they are a consistent finding in patients with ALF [42, 43]; similar to the case of ACLF, they reflect activation and injury of vascular endothelium [44]. Other investigators have confirmed these findings using TEG [45], and have shown that thrombin generation in the presence of TM in ALF patients is similar to normal healthy controls [46, 47].

These data suggest that patients with ALF generally maintain rebalanced hemostasis and that mechanisms to compensate for the profound deficiency of pro-coagulant coagulation factors must exist. Consistent with the observations by Tripodi and others in stable cirrhosis, pro- and anticoagulant, liver-derived coagulation factors decrease proportionally with increasing liver failure [42]. Profound activation of the SIRS by the cytokine storm which follows the primary liver injury appears to be a major driver of compensation, stimulating endothelial release of factor VIII and vWF. The SIRS may also contribute to rebalanced hemostasis by activating platelets, shedding pro-coagulant MPs into the circulation [41]. MPs are everted fragments (< 1 μm) of plasma membrane derived from many cell types in response to the SIRS [48]. The eversion process exposes phosphatidylserine, which activates the coagulation cascade synergistically with tissue factor (TF) [49]. As shown in Suppl Fig. 9, MPTF-associated pro-coagulant activity was 40-fold higher in patients with ALF compared to normal healthy controls.

A tendency toward decreased fibrinolysis in patients with ALF may also tip the balance toward hypercoagulability despite low fibrinogen concentrations. Patients with ALF have been suggested to develop disseminated intravascular coagulation (DIC) [50]; however, ALF patients regularly develop very high factor VIII levels, suggesting that classical DIC does not usually occur. In fact, clot lysis in vitro is delayed in most patients with ALF compared to healthy controls [46].

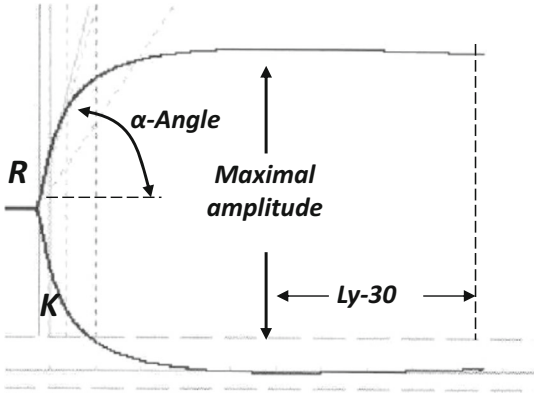
TEG analysis of whole blood from patients with ALF has suggested relative hypercoagulability in 25–35% [42, 45]. Similar to the case of cirrhosis, local hypercoagulability within the portal microcirculation may result in a secondary ischemic injury after the original insult by an acetaminophen overdose [51]. Peripheral hypercoagulability may also contribute to tissue hypoxia, lactic acidosis, and MOSF, caused in part by thrombi in the microcirculation [52]. Although gross thrombotic events have not been emphasized in large series of the ALF syndrome and are currently being studied by the ALF Study Group, microthrombosis of the hepatic and peripheral vasculature may be an unrecognized contributor to the pathogenesis of the syndrome.

Management of abnormal hemostasis in patients with advanced liver disease

The management of hemostasis in patients with cirrhosis or ALF has not been rigorously studied. Moreover, there are no randomized, prospective studies which show that withholding plasma or platelet transfusions before invasive procedures is safe. Studies to guide the clinician have thus

Table 3 Use of thromboelastography (TEG) to define the state of hemostasis in whole blood from patients with acute liver injury/failure

TEG parameter	Phase of clot formation	Normal range	ALI/ALF (N = 51)
R-time (min)	Latency	2.5–7.5	4.7 ± 1.9
K-time (min)	Fibrin kinetics	0.8–2.8	1.7 [0.8–20.0]
α-angle (°)	Fibrin kinetics	55.2–78.4	63.7 ± 12.2
Maximum amplitude (mm)	Clot firmness	50.6–69.4	55.0 ± 10.9
Lysis 30 (%)	Fibrinolysis	0.0–7.5	0.0 [0.0–2.1]



Mean/median TEG parameters in 51 patients with ALI/ALF, and normal values of these parameters (left panel). Representative TEG tracing from a patient with ALF due to an acetaminophen overdose. The tracing shows a hypercoagulable profile despite an INR of 4.2 and factor VII level of 4% of normal (adapted from: Stravitz et al. [42])

lagged well behind the in vitro studies discussed above. The following section will discuss prophylaxis against, and management considerations of, both bleeding and thrombotic complications in patients with advanced liver disease. Considerations will be cautiously applied in patients with ACLF and ALF, where very scant information is available.

Prevention and management of bleeding in patients with cirrhosis

One of the only attempts to systematically explore the safety of withholding blood products before invasive procedures in patients with stable cirrhosis was recently reported in 60 patients with a "significant coagulopathy", defined as an INR > 1.8 and/or platelet count $< 50 \times 10^9$/l [53]. Patients were randomized to receive "standard-of-care" plasma and/or platelet transfusion per hospital protocol, or a "TEG group", who received plasma and/or platelets only when they met specific abnormal TEG parameters. Only 17% of patients in the TEG group received a blood product transfusion vs. 100% of the standard-of-care group, with no difference in the rare occurrence of procedure-related bleeding complications (3.3% in the standard-of-care group vs. none in the TEG group; $p = 0.313$), or in survival. These intriguing but preliminary data suggest that many patients with stable cirrhosis may receive prophylactic transfusions of blood products before invasive procedures unnecessarily.

Red blood cell (RBC) transfusion in patients with cirrhosis has been recommended when the hemoglobin is < 8 g/dl [54]. Concern of rebound portal hypertension when post-transfusion hemoglobin exceeds 8 g/dl was shown in experimental models, in which rebleeding and mortality increased [55]. A similar caution has been raised with plasma infusion to correct the INR [56]. Conversely, severe anemia can itself exacerbate bleeding, since RBCs occupy a large proportion of blood volume, and their deficiency can theoretically redistribute platelets away from a defect in the endothelium. A landmark, randomized, controlled study of 921 patients with severe acute upper gastrointestinal hemorrhage (31% of whom had cirrhosis and ~ 25% bleeding from varices) has attempted to address the lower limit at which patients should receive RBC transfusions. Half of patients received RBC with a restrictive strategy (hemoglobin threshold for transfusion 7 g/dl with a target range for the post-transfusion hemoglobin 7–9 g/dl), and the other half received RBC according to a liberal strategy (hemoglobin threshold 9 g/dl; target range 9–11 g/dl) [57]. Patients managed under the restrictive strategy had lower death and rebleeding

rates; variceal rebleeding was 50% lower under the restrictive strategy. These data imply that RBC transfusion is important to restore rebalanced hemostasis in patients with cirrhosis, but should not be administered liberally to avoid exacerbating portal hypertension.

Figure 3 proposes an algorithm for managing abnormal hemostasis in a patient with stable cirrhosis who requires an invasive procedure. There are no data to support a threshold for correcting the INR with plasma, no relationship of the INR to post-biopsy bleeding, and stable patients usually have adequate pro-coagulant factors and rebalanced hemostasis. Therefore, it is unclear whether plasma infusion will decrease the risk of bleeding complications in this patient population. However, based upon in vitro studies [10] and in vivo correlations [11], a platelet count of $< 60 \times 10^9$/l may warrant the transfusion of platelets. Similarly, a plasma fibrinogen concentration of < 100 mg/dl may warrant repletion with cryoprecipitate or fibrinogen concentrate [35, 58]. The latter may be preferred over the former, since cryoprecipitate contains significant concentrations of vWF and FVIII, which are usually elevated in patients with cirrhosis, and Lisman et al. [59] have recently suggested that fibrinogen concentrate significantly improves hemostasis in patients with cirrhosis more than other pro-hemostatic agents in common use. For the reasons outlined above, a hemoglobin of < 7 g/dl warrants RBC transfusion [57]. Modification of this algorithm should be considered in a patient with clinical features which may contribute to the destabilization of hemostasis (e.g., renal failure or infection).

In Fig. 4, a patient with unstable cirrhosis and active bleeding requires treatment to achieve hemostasis. Since active bleeding exacerbates the preexisting deficiency of liver-derived, pro-hemostatic factors, plasma infusion is reasonable. Again, there is no recommendation of a threshold INR to administer plasma, and no goal of treatment. As for the prophylactic algorithm discussed above, active, clinically significant bleeding should also prompt consideration of platelets, fibrinogen concentrate, and RBC. Instead of the aforementioned guidelines for repletion before invasive procedures, however, the platelet count of $\geq 60 \times 10^9$/l, fibrinogen ≥ 100 mg/dl, and hemoglobin ≥ 7 g/dl should be viewed as goals of treatment rather than thresholds for treatment during active bleeding; in practice, the acuity of the clinical situation would seem to render thresholds for repletion irrelevant.

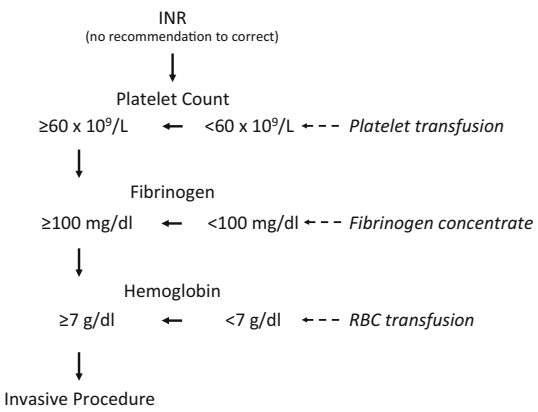


Fig. 3 Proposed algorithm for managing abnormal hemostasis in patients with cirrhosis prior to high-risk invasive procedures

Management of thrombosis in patients with cirrhosis

General guidelines for the prophylaxis against, and treatment of, thrombotic complications in patients with cirrhosis are on-going. Increasingly, there is general agreement that patients with cirrhosis, who are not actively bleeding or admitted for bleeding, should receive VTE prophylaxis [60]. PVT usually presents subclinically, and is discovered during Doppler ultrasound during surveillance for HCC (Fig. 5). In patients with newly identified PVT, cross-sectional imaging and angiography should be performed to confirm the diagnosis, define the extent of thrombosis (both anatomical and cross-sectional degree of occlusion), and to rule out malignant venous thrombosis. The decision to anticoagulate is not straight-forward, and multiple issues require consideration. The chronicity of thrombosis is important, because its presence for > 6 months suggests that anticoagulation will not be effective in achieving recanalization [61]. The degree to which the thrombus occludes the portal vein is important, because non-occlusive thrombi spontaneously recanalize in up to

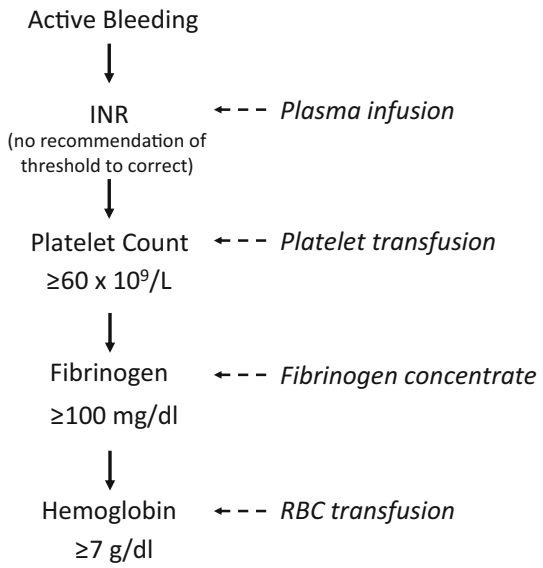


Fig. 4 Proposed algorithm for managing abnormal hemostasis in patients with cirrhosis and active bleeding

75% [24, 62]. Propagation over time, especially into the superior mesenteric vein, is indication for anticoagulation, since liver transplantation may be precluded in the event of complete porto-mesenteric thrombosis. The presence of gut ischemia due to porto-mesenteric thrombosis can be life-threatening, and represents another indication for urgent anticoagulation.

Loffredo et al. [62] have recently summarized the available data on safety and efficacy of anticoagulation for PVT in cirrhosis. Most studies used low-molecular-weight heparins (LMWH) with or without conversion to a vitamin K antagonist (warfarin). Complete recanalization occurred in 36–75% of patients; 17–53% failed to achieve recanalization. Bleeding complications ascribed to anticoagulants occurred in 5–27% of patients, but bleeding death was not observed in any study. Other studies have also repeatedly demonstrated that anticoagulation of PVT is safe and reasonably effective in selected patients, and actually decreased the incidence of portal hypertensive bleeding [23]. A recent meta-analysis of 6 studies compared outcomes of anticoagulation vs. no anticoagulation in PVT. Complete recanalization of the portal vein occurred 4.8-fold more commonly in those anticoagulated, while the odds ratio of variceal bleeding was only 0.23 compared to non-anticoagulated patients ($p = 0.04$) (Suppl Fig. 10) [62]. Insertion of transjugular intrahepatic porto-systemic shunts has also been tested to reestablish flow and lower portal pressure in cases where anticoagulation has not resulted in recanalization [61, 63], but has not been studied in a randomized fashion [64].

Finally, the possibility that anticoagulant use might increase the severity (rather than the incidence) of gastrointestinal bleeding has also been recently explored [65]. Anticoagulated patients with cirrhosis admitted for upper gastrointestinal bleeding were matched 1:2 with non-anticoagulated patients with bleeding and a similar severity of liver disease. The severity of bleeding in the two groups was similar by all parameters measured, suggesting that anticoagulation may not exacerbate the severity of bleeding in cirrhosis, should it occur.

The choice of anticoagulant and their dosing has not been systematically studied in patients with cirrhosis and thrombosis, but poses challenges in terms of safety and efficacy. Since vitamin K-dependent coagulation factors are low, it has not been determined how to safely dose warfarin in cirrhotic patients with elevated baseline INR. Anticoagulation with enoxaparin has been suggested to be both more [66] and less [67] effective in patients with cirrhosis in proportion to the severity of liver failure compared to controls, and requires clarification before dosing recommendations can be made with confidence. Renal failure complicating cirrhosis may also increase the potency of enoxaparin. Thus, it is not clear how to dose heparin/LMWH safely in patients with cirrhosis. Direct factor Xa inhibitors (apixaban and rivaroxaban) may have a safety profile similar to warfarin in a small pilot study of cirrhotics [68], but also may be less potent in patients with cirrhosis compared to healthy controls [69]. Obviously, additional studies are needed to define how to use anticoagulants in patients with cirrhosis, and which patient is at particular risk of bleeding complications from their use.

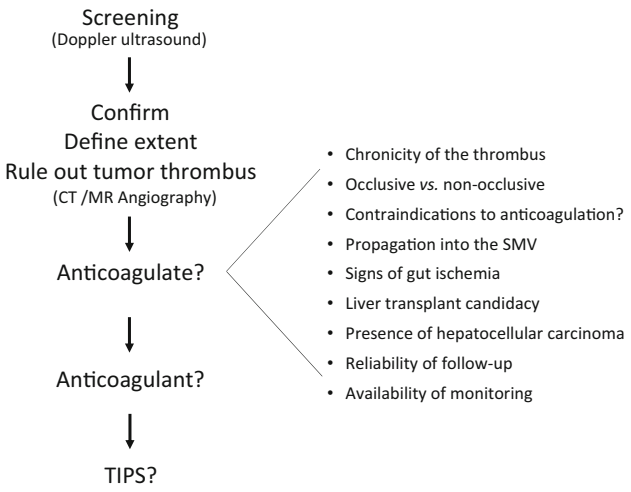


Fig. 5 Proposed algorithm for managing patients with portal venous thrombosis in patients with cirrhosis

Management of bleeding and thrombosis in ALF

There are essentially no data to guide clinicians in administering blood products before an invasive procedure or during an active bleeding episode in patients with ALF. Therefore, the algorithms presented in Figs. 3 and 4 may be reasonable general guidelines. As is the case with cirrhosis, the degree of risk of an invasive procedure must be taken into account, particularly before insertion of ICP monitors, which are associated with rare bleeding complications ($\sim$ 5%) but high mortality (50%) [37]. The assessment of risk should particularly consider the platelet count, which is associated with bleeding risk in ALF, rather than the INR, which is not [37].

The decision to transfuse plasma in patients with ALF needs to be carefully weighed against the fact that this measure will obfuscate the most important prognostic indicator of spontaneous recovery of the liver: the trend in INR. The ALF Study Group has also recently shown that patients who received any blood component in the first 7 days after admission had a 50% increase in death or liver transplantation at day 21 [37], raising the possibility that transfusions cause harm.

Although the algorithm in Fig. 3 may be reasonable before high-risk invasive procedures in cirrhosis, a defined volume of plasma should probably be considered in patients with ALF, since the latter usually have lower pro-coagulant, liver-derived coagulation factor levels than the former. A goal INR is not practical as it is often unattainable and risks volume overload; instead, ~ 2 units of plasma transfused within ~ 1 h of the procedure might be considered, since this strategy repletes pro-coagulant factors to achieve a minimal level to support thrombin generation. In treating patients with evidence of bleeding (Fig. 4), transfusions of plasma and platelets should be reserved for clinically significant bleeding, not the frequent occurrence of coffee grounds per nasogastric tube. Although small series have advocated the use of rVIIa before high-risk procedures such as ICP monitor placement [70], serious thrombotic complications of rFVIIa have been reported in patients with ALF [71].

The use of anticoagulants in patients with ALF is generally based upon local experience. Citrate has been avoided during RRT because of its decreased metabolism by the liver, but is probably safe [72]. The use of heparin during RRT is also probably safe in patients with ALF, although its efficacy may be impaired due to low AT levels. VTE prophylaxis should be strongly considered in patients with ALF. Pneumatic compression devices may be more appealing to clinicians in the setting of renal failure or severe thrombocytopenia, but low-dose heparins have been used without complications (RTS, personal observations).

Conclusion and perspectives

In conclusion, patients with stable cirrhosis appear to achieve rebalanced hemostasis. Portal hypertensive bleeding occurs due to portal pressure, not deficient coagulation. However, hemostasis in patients with severe acute or chronic liver disease is in a fragile state of compensation, the balance of which may be tipped toward bleeding or thrombosis by a number of precipitating factors. In the last stages of ACLF and ALF, the balance appears to be strongly tipped toward a bleeding diathesis. Further clinical studies demonstrating safety will be needed before clinicians will change their practice and consider withholding pro-coagulant therapies before high-risk invasive procedures. Further studies are also urgently needed to determine whether blood product transfusions cause harm in patients with stable acute or chronic liver disease, since tipping the balance further toward hypercoagulability may contribute to the pathogenesis of liver injury and complications of both syndromes.

Compliance with ethical standards

This review article does not contain any original data, only previously published studies with human and/or animal subjects, previously vetted by appropriate Institutional Review Boards.

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