Bleeding and Thrombotic Complications in Patients With Cirrhosis: A State-of-the-Art Appraisal

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Much has evolved over the past 25 years regarding our understanding of the coagulopathy of liver disease. Paradoxically, this form of coagulopathy is relatively hypercoagulability despite the common clinical impression of a hemorrhagic tendency. The latter is largely driven by portal-mesenteric venous pressure (ie, portal hypertension) and has little to do with hemostatic pathways. It cannot be emphasized enough that the INR does not offer a meaningful measure in this situation and may lead to interventions such as fresh frozen plasma that can actually worsen portal pressure and hence pressure-driven bleeding. With regard to procedure-related bleeding, we point out substantial differences in the definition of high-risk procedures and propose a new operational definition dependent on the applicability of local hemostatic measures, although this requires further investigation. The common occurrence of venous thrombosis in these patients requires careful consideration of hemostatic pathways and overall risk and benefit of intervention. The decision regarding anticoagulation therapy needs to be driven not only by a global assessment including history of non–portal hypertensive–related bleeding, but also by fall risk which can result in head trauma in patients prone to encephalopathy. This is probably best estimated by frailty but has yet to be adequately investigated. In the background of these concerns, several superimposed and complex conditions including infections and renal dysfunction should be taken into account. Inherited forms of thrombophilia in the setting of cirrhosis perhaps do not outweigh the thrombophilia inherent to liver disease but warrant further consideration.

Keywords: Hemorrhage; Thrombus; Liver; Coagulation; Bleeding.

Concepts Regarding Hemostatic Balance In Patients With Cirrhosis

Our understanding of coagulation disorders in liver disease patients has significantly evolved over the past 25 years. At the crux of these changes is our perception of the ubiquitous laboratory test called the international normalized ratio (INR). The test is derived from the prothrombin time (PT), which reflects the activity of liver-derived clotting factors I, II, V, VII, and X and the term normalization that refers to the results being adjusted among patients treated with vitamin K antagonists (VKAs) (such as warfarin) to account for variation in the activity of proprietary thromboplastins—a key reagent in measuring the PT. Bleeding in liver disease patients is a common problem, for example in variceal hemorrhage or possibly as a procedure-related complication. Because the liver synthesizes most of the key clotting factors, prolongation of the PT and hence the INR is common in patients with liver dysfunction. A relationship between a prolonged PT/INR and clinical bleeding in liver disease seemed obvious enough that for decades this was passed down through generations of trainees essentially as dogma through all fields of medicine. As a result, the emergence of data that convincingly refuted the apparent relationship has only slowly been taken up beyond the immediate fields of hepatology and hematology.

Historical Context

It was a convergence of developments around the turn of the century that underpinned these changing concepts of cirrhotic coagulopathy. These developments included the emergence of a more global and practical view of the clotting cascade in the cell-based model of hemostasis and the subsequent development of recombinant activated factor VII.[1] Although the agent did not become a significantly useful tool for bleeding in cirrhosis, its development helped to shift emphasis away from the older notion of the intrinsic and extrinsic

Abbreviations used in this paper: **DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PT, prothrombin time; PVT, portal vein thrombosis; TEG, thromboelastography; TIPS, transjugular intrahepatic portosystemic shunt; VKA, vitamin K antagonist; VTE, venous thromboembolism; vWf, von Willebrand factor.**

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hemostatic pathways to newer and more global concepts of the clotting cascade in the cell-based model of hemostasis.[1] Seminal work from Armando Tripodi and his team, further described subsequently, also raised questions about the interpretation of a number of the conventional tests of hemostasis in cirrhosis patients. In addition, work from Ian Wanless and his team raised the question of an intrahepatic thrombotic process in the development of organ atrophy and resultant clinical deterioration.[2] The first international meeting of the Coagulation in Liver Disease group in 2005 brought together many of these clinical investigators from diverse backgrounds to share data and experiences.[3]

Seminal Papers in the Field: Hypercoagulability in Cirrhosis

Tripodi and colleagues, demonstrated that the acquired deficiency of liver-synthesized protein C in cirrhosis combined with the preserved function of its cofactor, endothelial-derived thrombomodulin, results in a relatively hypercoagulable state measurable with the thrombin generation assay performed with and without thrombomodulin.[4,5] This work also clearly demonstrated the deficiencies of the INR as a measure of hemostatic pathways in liver disease, as the PT/INR is dependent only on liver-derived procoagulant factors and does not take into account the significant deficiencies of liver-derived anticoagulant factors such as protein C. Around this time, Trotter and colleagues demonstrated remarkable interlaboratory variation in the PT/INR of patients with cirrhosis depending on use of various commercially available thromboplastins normalized to warfarin-treated patients, rather than liver disease patients.[6] This led to further studies that demonstrated less variation between clinical labs if thromboplastin activity is normalized to a panel of cirrhosis patients (known as the INR^{Liver}) rather than warfarin-treated patients.[7,8] While the INR^{Liver} never caught on as a practical clinical test, these studies also raised as yet unresolved concerns about interlaboratory variation in the Model of End-Stage Liver Disease score, which includes INR as a variable and is widely used to guide assessment of disease severity and organ allocation. Another key early development in this field was the demonstration by Lisman and colleagues that the commonly encountered condition of thrombocytopenia in cirrhosis, due usually to hypersplenism, is significantly offset by the increase in endothelial derived von Willebrand factor (vWf) which favors platelet hemostatic activity at the site of vascular breach.[9] Other factors that appear to contribute to a relative state of hypercoagulability include an acquired deficiency of liver-derived antithrombin and elevated endothelial-derived factor VIII, which could relate to the vasodilatory state of cirrhosis.[10]

Rebalanced Hemostasis

Emerging from these milestones was the concept of a rebalanced hemostatic pathway in cirrhosis, which may actually be hypercoagulable. This is especially apparent in the common condition of cirrhotic portal vein thrombosis (PVT) and in the occurrence of deep vein thrombosis (DVT) in hospitalized liver disease patients.[11–13] A provocative publication has questioned hypercoagulability as a mechanism of PVT and can be viewed as a valid critique of emerging concepts, but we find that the current weight of evidence favors hypercoagulability as a significant contributing factor in PVT.[14] It is our opinion that cirrhotic PVT can be viewed as Virchow's triad with stasis of flow due to the same factors causing portal hypertension, endothelial injury due to the underlying liver disease, and the hypercoagulability of cirrhosis including an acquired protein C deficiency and other factors delineated previously such as elevated endothelial-derived vWf and factor VIII and decreased liver-derived antithrombin (Figure 1). Interestingly, non-O blood type blood type, which is a known risk factor for peripheral DVT due to a relationship with vWf and factor VIII activity, was not evident as a risk in cirrhotic PVT in one study.[15] The magnitude of the change in other factors may explain this, but further study is needed for this apparent disconnect between PVT and peripheral DVT. Similarly, the clinical relevance of factor ratios (such as the factor VIII-to-protein C ratio) to the hypercoagulable state of cirrhosis and PVT has been critically questioned and reflects the complexity of this topic with multiple interacting variables.[16] The basic sciences have also offered potential pathways worthy of clinical investigation in the future, including the role of neutrophil activation and their interaction with platelet activity, the P-selectin pathway, and the oxidative stress mechanisms via arachidonic acid metabolism to isoprostanes, which well may interact with very important variables of platelet lipid metabolism.[17–19] These pathways remain to be more fully explored. However, and perhaps most importantly, as a result of these changes, intrahepatic small vessel thrombotic disease has been implicated in organ atrophy and resulting clinical progression of cirrhosis in a process dubbed parenchymal extinction.[2] The latter has further led to a promising study of prophylactic anticoagulant therapy in cirrhosis, which warrants further study.[20]

The Cirrhotic Bleeding Phenotype: The Clinical Paradox

Despite the presence of a rebalanced hemostatic system or even a relatively hypercoagulable state in compensated cirrhosis, most clinicians have experienced significant bleeding in this patient population. However, it should be pointed out that bleeding in this

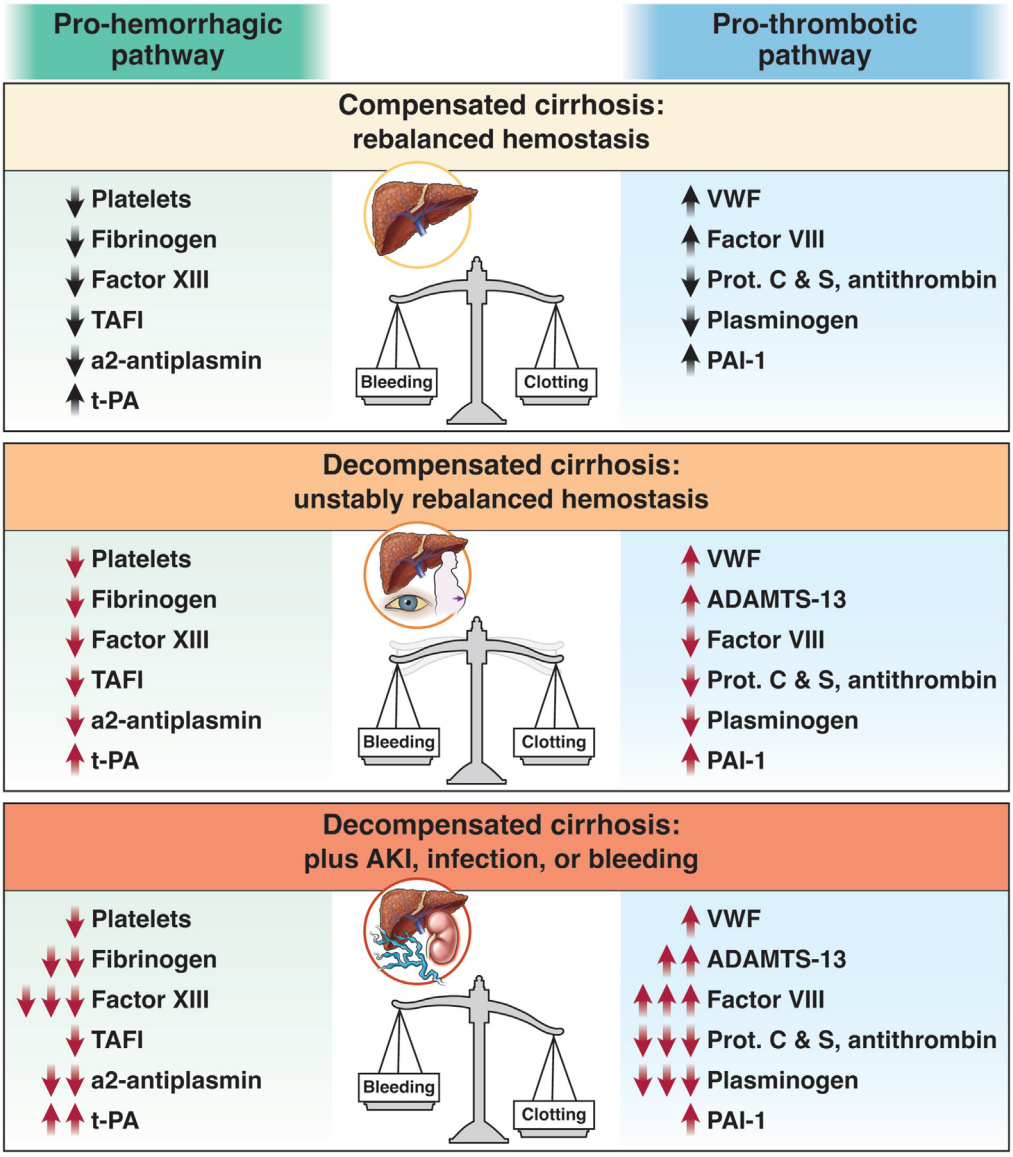

Figure 1. Hemostatic balance in patients with compensated cirrhosis, decompensated cirrhosis, or decompensated cirrhosis with complications (acute kidney injury [AKI], infection, bleeding). In compensated cirrhosis, the parallel changes in both pro- and antihemostatic pathways result in a rebalanced hemostatic state. With advancing disease severity, the ratio of pro- vs anticoagulant drivers increases progressively, resulting in higher hemostatic imbalance, tipping toward hypercoagulability, and a more fragile rebalanced state. This is further worsened by clinical events like AKI, bleeding, or infection. These relative changes are discussed in greater detail in the narrative. ADAMTS-13, A disintegrin and metalloprotease with thrombospondin-1 domain, member 13; AKI, acute kidney insufficiency; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue plasminogen activator; TAFI, thrombin activatable fibrinolysis inhibitor.

situation is usually pressure-driven from portal hypertension with little influence by hemostatic mechanisms, save perhaps for the well-known platelet plug sign at the site of a varix rupture.[21] It should also be noted that efforts to correct the PT/INR with plasma may actually exacerbate portal hypertension and, as noted previously, because the PT/INR is inherently not a reflection of the rebalanced clotting cascade in cirrhosis and because of interlaboratory variation, a target INR simply does not exist.

The Challenge of Hyperfibrinolysis

Another more controversial form of bleeding in patients with cirrhosis is the condition of hyperfibrinolysis or premature clot dissolution, characterized clinically by diffuse mucosal or puncture wound bleeding, usually in severely ill and decompensated patients.[22] Although clinically apparent and possibly responsive to antifibrinolytic therapy, laboratory demonstration of this condition has proven to be elusive even with global viscoelastic testing (such as thromboelastography [TEG] or thromboelastometry), for the native TEG, wherein TEG is conducted without use of clot stimulators.[23,24] The latter has been repeatedly reported on by Burroughs et al using unconventional performance of the TEG for a full hour without use of clot stimulators, in contrast to the commercial test instructions (A. Burroughs, October 01, 2011, personal communication). Paradoxically, in vitro studies of clot lysis in severely ill patients and decompensated cirrhosis patients have shown that formed clots appear to be resistant to normal clot lysis possibly mediated by oxidatively modified forms of fibrinogen (ie, a form of dysfibrinogen).[25,26] This issue remains unresolved, but given the clinical appearance

of patients with diffuse mucosal and puncture wound bleeding and response to antifibrinolytic therapy, it seems likely that patient selection for advanced blood study or limitations of laboratory methodology remain as obstacles to a better understanding of this condition. Nearly all body cavities (oral, biliary, urinary, and peritoneal for example) possess fibrinolytic capacity, which is advantageous for inappropriate clot formation and clot remodeling. Recent literature has also implicated ascites fluid as a potential factor in this process as was suggested many years ago.[27]

Other Significant Factors

Conditions often present in patients with decompensated liver disease, including renal failure, systemic infections, severe anemia, and volume overload, further add to the complexity of the concepts of a rebalanced hemostatic system in stable cirrhosis.[24,28] These variables present the clinician with a set of wild cards that require recognition of their importance and individualized intervention. In general, systemic infection and renal failure appear to add to bleeding risk. Early studies have indicated that systemic infection is associated with an anticoagulant effect as a result of endothelial release of heparin-like substances (endogenous heparinoids).[29] More recent work has indicated that systemic infection may both exacerbate hypercoagulability and hypocoagulability due to opposing effects on clotting factors vs platelet aggregation.[30] Coexistent renal dysfunction adds even greater complexity due to the possible effects of volume expansion on portal hypertension and engorgement of the venous vascular bed including the mesenteric venous collaterals and possibly impaired platelet function in uremia. More specific hemostatic changes have also been observed that may promote bleeding due to reduction of factor XIII activity, which facilitates crosslinking of fibrin leading to a stronger clot.[28] Basic science studies also suggest potential interactions with neutrophil activity and platelets, platelet fatty acid metabolism, and other potentially important pathways that may require eventually clinical translation.[31,32] Together, these conditions indicate that patient management must be multifaceted and individualized and especially adaptable to a potentially changing situations. No single test or measure can capture this complexity, notably the INR.

The Prevention And Treatment Of Bleeding Complications In Patients With Cirrhosis

This section focuses on bleeding occurring following an injury or an intervention in patients with cirrhosis. Bleeding events related to variceal bleeding will not be addressed here, as these events are generally related more to hemodynamic changes (mainly portal-mesenteric hypertension), rather than to hemostasis alteration. This is illustrated by the efficacy of vasoactive drugs (eg, octreotide) and the absence of efficacy of procoagulant drugs targeting hemostatic pathways (eg, recombinant factor VIIa) in this setting (see the following). We recognize that these entities are not always entirely separable, but here we have focused on hemostatic pathways rather than portal-mesenteric hypertension with pressure-driven bleeding. More information on this topic is anticipated soon from a prospective multicenter study known as PROC-BLeeD (Bleeding in Hospitalized Patients With Liver Disease Undergoing Invasive Procedures, NCT04076605).[33]

Prevention of Bleeding Complications: Identification of Patients at Risk

Iatrogenic bleeding is particularly problematic, as it carries risk not only for patient morbidity, but also for provider liability.[3] Prevention of bleeding complications first requires an assessment of the risk of bleeding, undertaken as soon as a procedure is scheduled and re-evaluated early before the procedure. The assessment should take into account the patient's history, the procedure and the results of laboratory tests, keeping in mind their limitations.

Patient's Medical History

When scheduling the procedure, a crucial step is seeking potentially modifiable risk factors for bleeding. This includes, the use and indications for anticoagulants or of antiplatelet agents, and also evidence of renal impairment or sepsis. Indeed, acute kidney injury is associated with a higher risk of procedure-related bleeding in patients with decompensated cirrhosis,[34] and successful treatment of acute kidney injury improves ex vivo measures of hemostasis.[35] The direct effect on bacterial infection on the risk of bleeding is less clear, but because infection is a well-known trigger for acute kidney injury in patients with cirrhosis, detecting and treating it before performing a procedure—when possible—seems reasonable.[34,35]

Procedure

Several classifications of bleeding risk associated with invasive procedures have been proposed.[36–39] However, they base risk stratification on the reported rate of bleeding, without considering patient populations undergoing these procedures. For instance, transjugular liver biopsies have been classified at the same level of

risk as percutaneous liver biopsies and percutaneous ablation of liver cancer in several of these classifications.[37,38] However, transjugular liver biopsies are performed in most centers in patients having severe coagulation abnormalities, while percutaneous liver biopsies or percutaneous ablation are restricted to patients with no or mild coagulation changes. The rate of bleeding and the risk of bleeding are not interchangeable concepts though. Second, while recent international guidelines used the same approach based on the frequency of major bleeding events following invasive procedures (threshold at 1.5%), they arrived at different conclusions: the European Association for the Study of the Liver guidelines classified both percutaneous and transjugular liver biopsies as procedures at low bleeding risk, the American Association for the Study of Liver Diseases classified both at high bleeding risk and the International Society on Thrombosis and Haemostasis classified transjugular liver biopsies at low risk and percutaneous liver biopsies at high risk.

In light of these differences, a more simple and operational classification is needed for appropriate management. We propose to consider low risk the procedures associated with a risk of bleeding that is easily detectable and controllable ("can we compress if the patient bleeds"). Low-risk procedures would then include most vascular procedures (except transjugular intrahepatic portosystemic shunt [TIPS] because of the numerous passages needed) and local interventions (eg, dental extraction). Conversely, when the site of the intervention is not easily accessed and poorly controllable, such as percutaneous intraperitoneal procedures or thoracentesis, one can consider the procedure at higher risk. In addition, the experience of the operator as well as the technical difficulty of the procedure are crucial factors and should also be considered.

Laboratory Test Results

Routine coagulation tests before invasive procedures usually include blood cell count, prothrombin time and, in some institutions, activated partial thromboplastin time (APTT). Yet, INR and APTT do not predict post-procedural bleeding in patients with cirrhosis undergoing invasive procedures.[36–38,40,41] Regarding platelet count, although studies do not allow the identification of a target platelet count reliably associated with risk of bleeding, a platelet count over 50×10^9/L is commonly viewed as a safe threshold for performing invasive procedures. Below that threshold, level of thrombocytopenia, type of procedure, and associated coagulation abnormalities should be considered. Regarding plasma fibrinogen concentration, levels <100 mg/dL are associated with spontaneous and procedure-related bleeding in patients with cirrhosis, but causal relationships are not established. Low fibrinogen levels may reflect critical illness and do not directly cause bleeding in most cases.[42,43]

Even if the value of routine coagulation tests to predict bleeding following invasive procedures is low, measuring them prior to an invasive procedure may serve to provide the clinician with a picture of the severity of liver disease as well as of the patient's baseline hemostatic status in the case of bleeding events, also prompting potential multidisciplinary evaluation in the case of extremely deranged, or unexpected, results.[37]

Viscoelastic Tests: TEG and Rotational Thromboelastometry

Four randomized control trials observed that the use of TEG and rotational thromboelastometry is associated with a decreased need for prophylactic blood transfusions.[44–48] However, these studies were not designed to determine whether viscoelastic tests can predict procedure-related bleeding. Moreover, reproducible thresholds for routine use are lacking. A recent prospective study including 302 patients undergoing liver biopsy assessed viscoelastic tests, together with an extensive hemostasis workup including Platelet Function Analyzer 100 (Siemens), thrombin generation assay, and plasma clot lysis time, and showed that none allowed prediction of liver biopsy–related bleeding.[49] A limitation of that study, however, was that the population was heterogeneous, including patients with and without cirrhosis and patients undergoing percutaneous and transjugular liver biopsy.

Strategies to Prevent Bleeding

There is lack of robust data on correcting coagulopathy before the performance of an invasive procedure in patients with cirrhosis. Table 1 summarizes recent guidelines published by international societies on that topic. Most societies agree on the following points regarding prevention of procedure related bleeding in patients with cirrhosis: (1) INR and APTT should not be corrected before an invasive procedure; (2) correction of fibrinogen deficiency does not seem relevant; (3) the antifibrinolytic drug tranexamic acid is not recommended, as it might favor venous thromboembolism (VTE) in patients with chronic liver disease[53]; (4) thrombocytopenia should not be corrected when platelet counts are above 50×10^9/L; and (5) correcting thrombocytopenia is reasonable when platelet count is below 20 or 30×10^9/L using infusion of platelet concentrates or thrombopoietin receptor agonists. Importantly, imaging guidance is now recommended for liver biopsy, central venous line placement, and jugular puncture for TIPS placement.[37]

Treatment of Active Bleeding Complications in Patients With Cirrhosis

If bleeding occurs following an invasive procedure, the crucial next step is to perform mechanical therapy

Table 1. Recommendations of Selected Professional Societies for Correction of Coagulation Parameters Prior To High-Risk Procedures In Patients With Cirrhosis

	BSG 2020[50]	ACG 2020[51]	AASLD 2021[38]	AGA 2021[52]	ISTH 2021[36]	EASL 2022[37]
Platelet count $\geq 50 \times 10^9$/L	Do not correct	Do not correct	Do not correct	Do not correct	Do not correct	Do not correct
Platelet count $<50 \times 10^9$/L	Transvenous approach recommended If not possible (lesional liver biopsy), platelet transfusion or thrombopoietin receptor agonists can be considered	Correct using high doses of platelet infusions; if the procedure is elective, use of thrombopoietin receptor agonists	No routine preprocedural correction	If severe thrombocytopenia and high-risk procedure discussion with a hematologist	Might correct in case of very high-risk surgery (eg, neurosurgery and intraocular surgery) and platelet count <30–50×10^9/L	If the platelet count is 20–50×10^9/L and local hemostasis is not possible, correction may be considered If the platelet count is $<20 \times 10^9$/L and local hemostasis not possible, correction should be considered
PT/INR	If INR >1.4, transvenous route recommended For percutaneous lesional biopsies, the INR should be <2.0 Fresh frozen plasma not recommended	Do not correct	Do not correct	Do not correct	Do not evaluate routinely	Do not correct
APTT	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Do not evaluate routinely	Not mentioned
Fibrinogen	No specific recommendation	No specific recommendation	Do not correct	Do not correct	Do not evaluate routinely	Do not correct
Viscoelastic tests	No specific recommendation	May be useful	Do not use routinely	No recommendation	Do not use routinely	Not possible to advise for or against their use

Adapted from Roberts et al.[36]

AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; APTT, activated partial thromboplastin time; BSG, British Society of Gastroenterology; EASL, European Association for the Study of the Liver; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time.

consisting of local compression, vascular embolization, or even surgical repair, especially if there is no component of portal hypertension, which should be treated if suspected. In addition, correcting some coagulation abnormalities might be useful, as detailed in Table 2. If there is clearly no component of portal hypertension, then the approach should be adapted to the coagulation profile of the patient and usually discussed with hematology; antifibrinolytic therapy can be considered.

Epidemiology And Management Of Thrombotic Complications In Cirrhosis

As discussed previously, the delicate hemostatic balance in patients with liver cirrhosis is easily altered by different factors during progression of chronic liver disease, such as portal hypertensive bleeding, infections, and acute kidney injury. It has become clear that the consequences are in general more on the thrombotic rather than the hemorrhagic side. This thrombophilic tendency manifests itself at the level of both the peripheral deep venous system and the portal-splanchnic circulation.

Prevalence and Incidence of Thrombotic Complications

The prevalence of DVT, VTE, and pulmonary embolism (PE) is variable in different series. There is substantial agreement that the adjusted hazard ratio is higher than in the general population, ranging from 1.7 to 2.0,[54,55] especially in younger patients (<45 years of age) and that the risk increases with the severity of the disease.[56] Like DVT, PVT is greatly influenced by liver disease severity.[57] The incidence at 1 year varies from 4.6% in Child-Pugh A[58] to 12.8%–16.6% in patients with mostly Child-Pugh B and C, with significant and continuing increase at 2 at 5 years, to reach 35%.[20,59]

As for arterial thrombosis, the risk of ischemic stroke is reported to be higher in patients with cirrhosis.[55] The risk of myocardial infarction, despite higher occurrence of coronary atherosclerosis in patients with cirrhosis, is increased only in decompensated patients.[40] However, both events are associated with increased mortality.[55]

Prevention of Thrombophilic Complications

Only a few studies have been performed on prophylaxis of thrombotic complications in chronic liver disease, likely due to the fear of precipitating hemorrhagic events, a concept that only recently has been disproved (Table 3). Despite that patients with cirrhosis at risk of DVT/PE can be identified using predictive scores like the Padua score (which has been validated in patients with cirrhosis),[75] these risk assessments and prophylactic strategies are generally underutilized in our opinion. The consequence of this is that the available data on DVT/PE prophylaxis have usually been retrospective. Still, existing evidence indicates that thromboprophylaxis with low-molecular-weight heparin (LMWH) or with direct oral anticoagulant (DOACs) in hospitalized patients

Table 2. Therapeutic Options to Improve Hemostasis in Patients With Cirrhosis and Active Bleeding (out of the Setting of Variceal Bleeding) in Case Local Hemostatic Maneuvers Are Not sufficient

	Statement	Rationale
Platelet transfusion	If thrombocytopenia (eg, if platelet count $<50 \times 10^9$/L)	Above $>50 \times 10^9$/L, bleeding events are very rare[41]
Thrombopoietin receptor agonists	Not appropriate for acute setting	Several days needed to increase platelet count
Fibrinogen concentrates	If fibrinogen <100 or 120 mg/dL	Fibrinogen consumption in case of bleeding and fibrinogen needed for clot stability
Fresh frozen plasma	Restricted to hemorrhagic shock to compensate blood loss	Large volume needed to ↑ coagulation factors
Prothrombin complex concentrate	Possibly in case of hemorrhagic shock	Beneficial in patients without liver disease undergoing cardiac surgery
Tranexamic acid	If hyperfibrinolysis	Requires caution if pathological clot such as portal vein thrombosis is present
Desmopressin (1-deamino-8-d-arginine vasopressin)	No	Desmopressin increases release of von Willebrand factor in the circulation, while circulating levels are already increased in cirrhosis
Recombinant activated factor VII	No	Efficacy not demonstrated; potentially associated with an increased rate of arterial thromboembolic events

(Child-Pugh A and B patients) has an acceptable safety profile.[76–79] However, efficacy is still to be confirmed.[37,80] Regarding PVT, only one study has been performed so far, comparing LMWH for 1 year with placebo.[20] Anticoagulation significantly decreased the rate of PVT, while survival and the rate of decompensation significantly improved. Of 2 confirmatory studies, one was prematurely terminated as the enrollment rate was too low (NCT02271295), and the other has completed enrollment but the results are yet to be released (NCT02643212). Further support of the possible favorable role of anticoagulation to prevent PVT has come from a network meta-analysis of 19 prophylactic studies after splenectomy, which shows that application of anticoagulation was more effective than no intervention, especially when applied early to prevent thrombosis of the portal venous system. LMWH was shown to be the most effective, followed by antithrombin.[81] Overall, the available data are not yet sufficient to support broad application of prophylactic anticoagulation; however, the influential Baveno VII workshop has recently revised the previous negative indications, suggesting that anticoagulation should not be discouraged in view of the possible reduction of adverse liver-related outcomes and improvement of overall survival.[82]

Therapy of DVT/VTE/PE (Venous Thrombotic Disease)

The available clinical studies assessing the effects of anticoagulation for the treatment of active venous thrombotic disease in patients with cirrhosis are limited to observational and retrospective case series (Table 3). With these limitations in mind, there is general agreement that all class of drugs (LMWH, VKA, DOACs) are safe,[83] and treatment was shown to be generally effective in preventing recurrence of major events such as VTE or ischemic stroke. According to the European Association for the Study of the Liver Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis, VKA, LMWH, and DOACs can be recommended for Child-Pugh A patients. In Child-Pugh B and C patients, LMWH is the drug of choice, while unfractionated heparin is the treatment of choice in case of renal failure. The recently published guidelines of the International Society on Thrombosis and Haemostasis[84] do not diverge from the previously mentionned guidelines, except for preference for LMWH or fondaparinux over unfractionated heparin even in case of renal impairment.

Therapy of Portal or Splanchnic Venous Thrombosis

Many studies have addressed the issue of treatment of splanchnic vein thrombosis or PVT (Table 3). From the methodological point of view, most have flaws, being retrospective and observational, and without a prespecified protocol. Nevertheless, an increasing number of meta-analyses or systematic reviews have analyzed in detail these studies,[74,85] also focusing on specific aspects such as bleeding.[66] The most recent of these meta-analyses have examined and compared results and safety not only of traditional anticoagulants (LMVH and VKA), but also of DOACs.[54,62,86] These reports also have methodological limitations, but there is general agreement that treated patients have higher rates of recanalization and lower rates of progression of thrombosis than untreated patients. Similar agreement exists on the efficacy of the different class of drugs in obtaining this result: VKA was less effective both when compared with LMWH[68] and with DOACs.[54,62,86] The latter class of drugs performed better than LMWH. Bleeding risk was acceptably low and similar for all 3 class of drugs, although individual studies indicated slightly higher risk for VKA,[87] and mortality was not significantly different in any of the studies. In general, these results have been consistent, indicating a lower rate of recurrent thrombosis, major bleeding, and mortality during anticoagulation. Notably, there are no controlled data regarding when to stop anticoagulation or whether it should be continued indefinitely due to recurrence risk. So far, long-term administration is recommended only for patients with cirrhosis listed for transplantation and in case of thrombosis progressing to the splanchnic veins. Inherited prothrombotic risks are another incompletely defined factor, although presently does not seem to be a major one.[82]

Assessment of the Risk Associated With Anticoagulants

Although the role of anticoagulants is expanding in the management of patients with cirrhosis, individual risk of bleeding needs to be carefully assessed at treatment initiation and also reconsidered in case of a clinical event. A recent meta-analysis on anticoagulation in patients with cirrhosis and PVT showed an advantage in terms of survival despite a higher occurrence of non–portal hypertensive bleeding.[61] Assessment should include not only history of non–portal hypertensive–related bleeding, but also fall risk in patients prone to encephalopathy, in frail patients, or in those who have an excessive alcohol consumption. Superimposed conditions including infections and renal dysfunction should also be taken into account.

Patients with PVT without cirrhosis and without major risk factors for thrombosis constitute a very different group with different pathophysiology.[13] In this group of patients, the recent RIPORT ("Xarelto Versus no Treatment for the Prevention of Recurrent Thrombosis in Patients With Chronic Portal Vein Thrombosis"; NCT02555111) randomized clinical trial showed that rivaroxaban 15 mg/d reduced

Table 3. Characteristics of Meta-Analysis Studies on Anticoagulation for Thromboprophylaxis and Therapy of Thrombotic Conditions in Cirrhosis

Author, Year	Study Design	Studies Evaluated	Population and Number of Patients Involved	Types of Anticoagulation	Type of DOAC Considered	Performance	Complications
Prophylaxis for VTE/DVT/PE							
Gomez Cuervo et al, 2013[60]	Systematic review and meta-analysis	3	Patients with cirrhosis at VTE risk: n = 1,057	LMWH, heparin	—	VTE: no difference between treated and control subjects	Nothing relevant
Prophylaxis for PVT							
Gomez Cuervo et al, 2013[60]	Systematic review and meta-analysis	2	Patients with cirrhosis at PVT risk: n = 103	LMWH	—	PVT prophylaxis: anticoagulation > no treatment	Nothing relevant
Therapy for PVT: studies without TIPS focusing on recanalization							
Guerrero et al, 2023[61]	Individual patient data meta-analysis	5 (observational)	Patients with cirrhosis with PVT: n = 500	VKA, LMWH	—	Improved survival in anticoagulation group No difference in recanalization	Non–portal hypertension–related bleeding, greater in the anticoagulation group
Koh et al, 2022[62]	Meta-analysis	11 (10 observational and 1 randomized trial)	Patients with cirrhosis with AF, VTE, PVT, or DVT: n = 551	VKA; DOACs	Apixaban, dabigatran, edoxaban, rivaroxaban	PVT recanalization and lower risk of PVT progression: DOAC > VKA	Bleeding risk and mortality: similar between DOACs and VKA
Chen et al, 2021[63]	Meta-analysis	36: 11 RCT, 25 observational	Patients with cirrhosis with PVT: n = 3,479	LMWH, VKA, DOACs, antithrombin III, aspirin	Apixaban, dabigatran, edoxaban, rivaroxaban	Recanalization: DOACs > traditional anticoagulants	Bleeding risk and mortality: no differences in treatment groups Bleeding events increased in prophylactic group
Ng et al, 2021[54]	Network meta-analysis and Single-arm meta-analysis	10: 3 RCT, 7 observational	Patients with cirrhosis with PVT Network: n = 527 Single arm: n = 200	LMWH, VKA, DOACs, antithrombin III	Apixaban, dabigatran, edoxaban, rivaroxaban	Recanalization: DOACs > LMWH > VKA	Bleeding risk: low and comparable among treatments
Gao et al, 2021[64]	Meta-analysis	8	Patients with cirrhosis with PVT: n = 225	VKA, LMWH, DOACs (n = 39)	Rivaroxaban, dabigatran	Recanalization: LMWH > VKA > no treatment	Bleeding risk: low and comparable among treatments
Wang et al, 2021[65]	Meta-analysis	33	Patients with cirrhosis with PVT: n = 1,696	VKA, LMWH	—	Recanalization: DOACs > VKA > LMWH > no treatment	Bleeding risk and mortality: low and comparable among treatments

Table 3. Continued

Author, Year	Study Design	Studies Evaluated	Population and Number of Patients Involved	Types of Anticoagulation	Type of DOAC Considered	Performance	Complications
Mohan et al, 2020[66]	Meta-analysis	17	Patients with cirrhosis with PVT 648 anticoagulation 96 control subjects	VKA, LMWH, DOACs	Rivaroxaban, edoxaban	Recanalization: DOACs > VKA > LMWH > no treatment	Bleeding risk: low and comparable among treatments
Ghazaleh et al, 2020[67]	Meta-analysis	9 (observational)	Patients with cirrhosis with PVT: n = 474	VKA, LMWH, sulodexide, no treatment	—	Recanalization: anticoagulation > no treatment	Bleeding risk: low and comparable among treatments
Loffredo et al, 2017[68]	Meta-analysis	8	Cirrhosis with PVT: n = 353	VKA, LMWH, no treatment	—	LMWH > VKA > no treatment	Bleeding risk and mortality: low among treated patients
Therapy for PVT: studies with TIPS focusing on recanalization							
Zhang et al. 2021[69]	Meta-analysis	12: 3 RCT, 9 observational	Cirrhosis with PVT: n = 460	—	—	Recanalization at 1 y = 77.7% TIPS: overall technical success = 94.6%	Hepatic encephalopathy: 16.4%
Davis et al. 2019[70]	Meta-analysis	7: 2 RCT, 5 observational	Cirrhosis with PVT: n = 327	VKA, LMWH, TIPS	—	Anticoagulation: recanalization = 47.2% TIPS: recanalization = 81.0%	Bleeding risk: low and comparable among treatments Mortality lower in anticoagulation
Rodrigues et al, 2018[71]	Meta-analysis	13: 3 RCT, 10 observational	Cirrhosis with PVT: n = 399	—	—	Recanalization at 1 y = 79.0% TIPS: overall technical success = 95.5%	Hepatic encephalopathy: 23.2%
Valentin et al, 2018[72]	Meta-analysis	18: 3 RCT, 15 observational	Cirrhosis with PVT: n = 447	—	—	Recanalization at 1 y = 84.4% TIPS: overall technical success = 86.7%	Hepatic encephalopathy: 25.3%

Table 3. Continued

Author, Year	Study Design	Studies Evaluated	Population and Number of Patients Involved	Types of Anticoagulation	Type of DOAC Considered	Performance	Complications
Therapy for splanchnic vein thrombosis: studies analyzing thrombosis recurrence							
Candeloro et al, 2022[73]	Meta-analysis	12	N = 2,525 Cirrhosis with PVT: n = 287	LMWH, UFH, fondaparinux, VKA, DOACs, antithrombin III	Apixaban, dabigatran, edoxaban, rivaroxaban	Reduced recurrent VTE: anticoagulant > no treatment	Bleeding risk: reduced in treated group
Valeriani et al, 2021[74]	Systematic review & Meta-analysis	26: 3 RCT, 23 observational	Cirrhosis with PVT: n = 1,475	LMWH, VKA, DOACs	Apixaban, dabigatran, edoxaban, rivaroxaban	Anticoagulation > no treatment: increased vein recanalization and lower thrombosis progression	Mortality lower in anticoagulation

Only meta-analyses mentioning the type of anticoagulant used have been included.
DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; RCT, randomized controlled trial; TIPS, transjugular intrahepatic portosystemic shunt; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

the incidence of VTE without increasing major bleeding.[88] These prospective results are in line with evidence showing that anticoagulants are safe in patients with portal hypertension; however, isolated PVT without underlying liver disease is a different type of problem without coagulation changes associated with cirrhosis.

Direct Portal Vein Intervention

An alternative approach in case of recurrent PVT has recently gained attention. The approach exploits TIPSS to obtain patency. TIPSS was most often placed via transjugular intrahepatic route, but percutaneous transhepatic, transsplenic, and transmesenteric routes have also been used to gain access to the portal venous system for endovascular interventions.[89] These interventions can be seen as addressing one key aspect of Virchow's triad of thrombotic disease: flow as opposed to stasis. Two systematic reviews and meta-analyses, including partially overlapping studies showed that this approach is feasible, effective, and safe, although often technically demanding.[71,72] As the number of randomized controlled studies analyzed was low, additional data should be acquired before considering this approach as first line instead of anticoagulation.

Conclusion

The last 25 years have seen impressive changes in our understanding of coagulation in patients with cirrhosis leading to changes in practice guidelines and patient management, toward less focus on bleeding and risks of anticoagulants and more attention to thrombosis and activation of coagulation. Yet, the balance between bleeding and thrombosis is definitely precarious in patients with cirrhosis so that patient management should be made on an individual basis taking into account patients' comorbidities and medical history. Perspectives in this field should include not only continuing the efforts in homogenizing practice and definitions, but also promoting randomized clinical trials to increase the level of applicable evidence.

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Conflicts of Interest
These authors disclose the following: Pierre-Emmanuel Rautou has received research funding from Terrafirma; served as a consultant for Hemostod, Mursla, Genfit, Boehringer Ingelheim, and Abbelight; and received speaker fees from Tillotts Pharma. Stephen H. Caldwell has received research support for sponsored trials from Gilead, GenFit, Durect, BMS, Inventiva, Madrigal, Zydus, AstraZeneca, Cour, Galectin, Exact, and Novo Nordisk, and royalties from Avvanos. Erica Villa discloses no conflicts.

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