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Position Paper

Hemostatic balance in patients with liver cirrhosis: Report of a consensus conference

Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)

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ABSTRACT

Patients with cirrhosis present with hemostatic alterations secondary to reduced availability of pro-coagulant and anti-coagulant factors. The net effect of these changes is a rebalanced hemostatic system. The Italian Association of the Study of the Liver (AISF) and the Italian Society of Internal Medicine (SIMI) promoted a consensus conference on the hemostatic balance in patients with cirrhosis. The consensus process started with the review of the literature by a scientific board of experts and ended with a formal consensus meeting in Rome in December 2014. The statements were graded according to quality of evidence and strength of recommendations, and approved by an independent jury. The statements presented here highlight strengths and weaknesses of current laboratory tests to assess bleeding and thrombotic risk in cirrhotic patients, the pathophysiology of hemostatic perturbations in this condition, and outline the optimal management of bleeding and thrombosis in patients with liver cirrhosis.

1. Introduction

Hemostatic alterations are common in patients with cirrhosis. For a long time it was believed that a defective synthesis of pro-coagulant factors together with thrombocytopenia increased the risk of bleeding but protected against thrombosis in these patients. Accordingly diagnostic and therapeutic invasive procedures in patients with cirrhosis were considered risk factors for bleeding. However, this belief has been challenged by evidence of a concomitant decrease of anti-coagulant factors. The net effect of these changes is a rebalanced hemostasis. However, this hemostatic profile is unstable, and patients can be tipped toward both bleeding and thrombosis under certain conditions [1–5]. Thus, there is growing evidence that proper understanding of the hemostatic pathways in liver disease requires a global perspective which account for the complexity of hemostasis, with dynamic interactions between pro-coagulant and anti-coagulant factors.

2. Methods

A consensus meeting promoted by the Italian Association for the Study of the Liver and the Italian Society of Internal Medicine was held to discuss limitations of current laboratory tests for the assessment of bleeding and thrombotic risk, and to review the management of bleeding and thrombosis in patients with cirrhosis. A scientific board of experts was initially appointed to identify relevant topics relating to alterations of coagulation in cirrhotics. Subsequently, relevant literature data pertaining to each of the 5 identified major topics was conducted by several ad hoc subcommittees of experts with the aim to highlight areas with high-quality and/or uncertainty; the sub-committee work ended with the formulation of several statements. The process ended with a formal consensus meeting held in Rome in December 5 and 6, 2004, when the statements were finalized, graded according to quality of evidence and strength of recommendations, and finally approved by an independent jury. The quality of evidences and strength of

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recommendations were graded according to the GRADE system (Table S1).

3. Laboratory tests to assess bleeding

3.1. Bleeding time

In patients with cirrhosis, bleeding time is prolonged [6], but the clinical meaning of this laboratory alteration is uncertain as values were not predictive of bleeding secondary to liver biopsy [7] or esophageal variceal rupture [8]. Even in settings other than cirrhosis, the test had no predictive value for bleeding [9]. Furthermore, a randomized clinical trial on patients with variceal bleeding aimed at testing the efficacy of desmopressin (a drug known to shorten the bleeding time) combined with terlipressin, was interrupted prematurely because of excess hemorrhagic events in the desmopressin arm [10].

Statement. ***Bleeding time should not be used in patients with cirrhosis as a screening test to predict the risk of esophageal varices bleeding or bleeding following invasive procedures (A2).***

3.2. Platelet count

Patients with cirrhosis present with variable degrees of thrombocytopenia [11] and increased levels of the adhesive protein von Willebrand factor (VWF) which facilitates in vitro platelets to adhere and aggregate normally [2]. When the platelet count was adjusted to a standard value of 100×10^9/L, platelet-rich plasma from patients with cirrhosis generated in vitro as much thrombin as that of healthy subjects [12]. Although the benefit of platelet infusion to avoid bleeding in cirrhotics has never been assessed in clinical trials, counts of 60×10^9/L are considered sufficient to secure in vitro thrombin generation at the lower reference limit [12]. In hepatitis C-related cirrhosis, platelet numbers of $\leq 60 \times 10^9$/L were associated with an increased risk of procedure-related bleeding [13]. The practice of transfusing one single adult platelet dose only to patients with cirrhosis and counts $<50 \times 10^9$/L undergoing variceal banding elevates circulating platelet counts only marginally, with no or little effect on thrombin generation and thromboelastometry [14].

Statement. ***Platelet counts $\geq 50 \times 109$/L are considered to ensure normal primary hemostasis (B).***

3.3. Prothrombin time

The prothrombin time (PT), with results expressed as international normalized ratio (INR), is the standard test to monitor therapy with vitamin K antagonists (VKA). In cirrhosis, PT prolongation parallels impairment of the synthetic capacity of the liver has been used to assess bleeding risk. However, increasing evidence suggests that PT (and other congener tests) poorly reflects the hemostatic balance in cirrhosis. In these patients, reduced levels of pro-coagulants are counteracted by a parallel reduction of their anti-coagulant counterparts [4]. The paradoxical prolongation of the PT, in spite of normal thrombin generation, stands to the fact that the PT is more sensitive to the reduction of pro-coagulants than to the reduction of anti-coagulants, especially of protein C. Protein C, which is reduced in cirrhosis, must be activated to express its full anti-coagulant activity. In addition, its main physiological activator, thrombomodulin, is located in endothelial cells but not in plasma nor in reagents used to estimate the PT. Previous observations are in line with the long lasting evidence that the PT is a poor predictor of peri- or post-operative bleeding in cirrhosis [15–22]. Furthermore, a powerful pro-hemostatic agent, such as recombinant activated factor VII (rFVIIa), although capable of considerably shortening the PT [23], proved to be ineffective to stop esophageal bleeding [23,24], or to reduce bleeding at surgery [25,26].

Statement. ***Current evidence does not support the use of PT values as predictors of bleeding or to monitor the effectiveness of hemostasis-modifying therapy in patients with cirrhosis (A2).***

3.4. Thromboelastometry/thromboelastography

Whole blood viscoelastic tests evaluate the kinetics of coagulation, from initial clot formation to final clot strength. The viscoelastic properties of blood components are assessed in vitro by the thromboelastometry/thromboelastography (ROTEM/TEG) techniques. Due to the reagents used for testing (i.e. citrated whole blood, which includes plasma, erythrocytes, leukocytes and platelets), these tests should, at least in principle, reflect the global coagulation occurring in vivo better than other conventional plasma-based tests. Although data from clinical trials are lacking, these tests are widely used in the setting of liver transplantation to manage major hemorrhage or to trigger blood transfusion. Even in this setting, the threshold values of ROTEM/TEG parameters for triggering transfusion of hemostatic agents (such as fresh frozen plasma), remains to be determined [27], even though in a randomized study significantly fewer units of fresh frozen plasma (FFP) or blood were needed at the time of liver transplantation in patients monitored by TEG [28]. These promising results warrant larger confirmatory studies.

Statement. ***The use of algorithms based on thromboelastometry/thromboelastography (ROTEM/TEG) may facilitate targeted transfusions with hemostatic agents, such as fresh frozen plasma, in patients undergoing liver transplantation or in those with severe bleeding (C2). However, the threshold values of these tests to target transfusion requirement need to be established in appropriate clinical trials.***

3.5. Thrombin generation assays

Thrombin generation assays (TGA) assess the time course of thrombin generation and its decay when plasma is triggered by small amounts of tissue factor and phospholipids. Because of their design, TGA approximate the in vivo coagulation balance better than conventional coagulation tests (PT/activated partial thromboplastin time [APTT]). When evaluated by TGA, patients with cirrhosis have the potential to generate as much thrombin as healthy subjects after thrombomodulin addition [1,4]. Patients with cirrhosis and relatively high levels of thrombin generation present with a hypercoagulable state in vitro [29] and may be at risk of thrombotic events. By the same token, patients with relatively low levels may be at increased hemorrhagic risk. However, clinical trials are warranted to test this hypothesis.

Statement. ***Thrombin generation assays are promising laboratory tools which may help stratify patients with cirrhosis at risk for hemorrhage or thrombosis (C2). Before their implementation in clinical practice is recommended effectiveness should be tested in clinical trials.***

3.6. Fibrinolysis

Under physiological conditions, plasminogen-to-plasmin conversion is regulated by profibrinolytic drivers [i.e., tissue plasminogen activator [t-PA], urokinase plasminogen activator and activated factor XII]. These effects are opposed by antifibrinolytic drivers (i.e., t-PA inhibitors (PAI-1), plasmin inhibitor (PI) and thrombin-activable fibrinolysis inhibitor (TAFI)]. Perturbations of this balance

may result in hyperfibrinolysis or hypofibrinolysis. Plasma hyperfibrinolysis has been reported in patients with cirrhosis [30], but its mechanism in bleeding is still debated [31] due to lack of adequate laboratory tests for its evaluation. Available observations are based on the evaluation of individual components of fibrinolysis, but not on the overall action of both pro- and anti-fibrinolytic drivers, as it occurs in vivo. Cirrhosis has been associated with laboratory changes suggesting hyperfibrinolysis (i.e., increased t-PA and reduced PI or TAFI), but also with changes suggesting hypofibrinolysis (i.e., reduced plasminogen and increased PAI). Despite conflicting data, the balance of fibrinolysis is likely restored by concomitant changes in the pro- and anti-fibrinolytic drivers [3,32,33].

Statement. ***Although hyperfibrinolysis may favor bleeding in patients with cirrhosis, the steps in fibrinolytic process cannot be assessed by currently available laboratory tests (C).***

4. Laboratory tests to assess a hypercoagulable state

4.1. Testing for thrombophilia

In the population without cirrhosis, congenital deficiencies of anti-coagulants or acquired increased levels of pro-coagulants, or both are risk factors for thrombosis. In patients with cirrhosis, thrombophilic parameters, such as anti-thrombin, protein C, protein S, the Leiden gain-of-function polymorphisms of factor V, or the prothrombin gene gain-of-function mutation have been investigated in order to assess their usefulness in stratifying patients at risk for portal vein thrombosis (PVT). A recent meta-analysis questioned the utility of anti-thrombin, protein C, and protein S levels to predict PVT [34], while measurement of congenital deficiencies of anticoagulants may be informative in patients with cirrhosis and a personal or familial history of thrombosis. Carriers of polymorphisms of factor V or prothrombin gene were at increased risk of PVT [35], as were those with increased levels of factor VIII [36]. Anti-phospholipid syndrome also carries a risk for thrombosis in the population without cirrhosis; however, the laboratory diagnosis of this syndrome which is based on phospholipid-dependent coagulation tests, is unreliable in patients with cirrhosis, who have abnormal coagulation tests at baseline. Anticardiolipin (aCL) and anti-Beta2-glycoprotein I (a-Beta2-GPI) might better serve to detect this condition.

Statement. ***Due to impairment of the liver synthetic function, anti-thrombin, protein C and protein S are abnormally low in patients with cirrhosis. Their levels (measured with standalone assays) should not be used to evaluate the risk of thrombosis (A1). In patients with cirrhosis and personal or familial history of thrombosis, evaluation of factor V Leiden, prothrombin gene polymorphisms, and factor VIII plasma levels may be useful in stratifying the risk of portal vein thrombosis (B2). The diagnosis of anti-phospholipid syndrome is currently hampered by the intrinsic limitations of coagulation tests in patients with cirrhosis (A). Searching for anti-cardiolipin and anti-beta2-glycoprotein seems promising for this purpose (C), but further investigation is required.***

4.2. Thrombin generation assays

The ratio of endogenous thrombin potential with or without thrombomodulin parallels the severity of cirrhosis, and correlates with increased levels of factor VIII, reduced levels of protein C, and their ratios [29]. These results were confirmed when, instead of thrombomodulin, Protac (a non-physiologic protein C activator) was used for testing [37]. Resistance to anti-coagulant action of thrombomodulin or Protac is recognized as a risk factor for venous thromboembolism in patients without cirrhosis. Whether or not this in vitro resistance might be associated with the risk of peripheral vein thrombosis or PVT in patients with cirrhosis is still unknown.

Statement. ***Thrombin generation assay with/without thrombomodulin or Protac might be useful to assess the risk for venous thromboembolism in patients with cirrhosis (C). Nevertheless, further investigations are needed before their use is recommended in clinical practice.***

5. Coagulation tests as prognostic markers

As most coagulation factors are synthesized by the liver, global and specific coagulation assays reliably indicate the severity of cirrhosis and patient prognosis. Both the Child-Turcotte-Pugh score (CTP) and the model for end stage liver disease (MELD), which incorporate the PT value in the models, proved to be effective in assessing survival. The assumption that in liver cirrhosis the INR yields the same numerical results when measured in different laboratories using different thromboplastins is still accepted [38]. However, depending on the thromboplastin used in the assay, the INR measured for an individual patient may vary across laboratories [39], thus introducing a bias into the CTP and MELD scores which may affect the priority for liver transplantation [40,41]. There have been attempts to solve this issue by two groups who proposed new systems for INR standardization: the INR-liver (valid for patients with cirrhosis) and the INR-VKA (valid for patient on VKA) [40,41]. These methods have not yet been endorsed by scientific societies or regulatory authorities.

Statement. ***The PT/INR test contributes to the Child-Turcotte-Pugh and model for end-stage liver disease (MELD) scores, and is considered a reliable index for grading the severity of liver impairment (A1). However, there is some concern about the reporting of this parameter using the common INR scale. Implementation of the INR-liver or any other effective system of standardization is warranted.***

6. Monitoring anti-thrombotic therapy

In patients with cirrhosis VTE may occur either in portal or peripheral veins [42,43]. When VTE occurs, the use of anti-coagulants (heparins and VKA) becomes an option. Anti-coagulation with s.c. LMWH or fondaparinux, or with intravenous unfractionated heparin (UFH) was initially recommended for acute VTE in non-liver disease patients. In patients with cirrhosis, a major concern regarding the use of heparins is the reduction of anti-thrombin, as parentally administered drugs need to bind antithrombin to exert their action. On the other hand, it has not yet been established whether in patients with cirrhosis the INR interval used in the general population for monitoring anti-coagulation, may be applied. Accordingly, laboratory monitoring and management of patients with cirrhosis while on anti-coagulants requires special expertise.

6.1. Unfractionated heparin

UHF is administered as intravenous injection and requires laboratory monitoring using the APTT assay, with a therapeutic interval set at 1.5–2.5 times prolongation over baseline. This interval depends heavily on the reagent/instrument used for testing. The 1.5–2.5 APTT value corresponds approximately to 0.3–0.7 U/mL of anti-Xa. However, as for the APTT, standardization of anti-Xa assays and their therapeutic intervals have not yet been established. Due to these as well as other limitations (e.g., heparin induced thrombocytopenia, osteoporosis, etc.), UFH use has been gradually replaced by LMWH.

Statement. ***When monitoring unfractionated heparin (UFH) therapy, the APTT test may vary between centers depending on the reagent locally used (C). Furthermore, APTT is often prolonged in cirrhosis, so UFH will probably be under-dosed when the criterion of 1.5-2.5 APTT prolongation over baseline is applied (C). Consequently, intravenous UFH is not recommended in cirrhosis (A1).***

6.2. Low molecular weight heparin (LMWH)

In patients without cirrhosis, LMWH is administered subcutaneously once daily or twice daily in a fixed dose for thromboprophylaxis, and a weight-adjusted dose for therapeutic purposes. Laboratory monitoring is not mandatory but is required in special circumstances, such as obesity, renal insufficiency or pregnancy. Fondaparinux is administered subcutaneously once daily in a fixed dose, and no laboratory monitoring is required. Thus, the main question is whether or not fixed- or weight-adjusted LMWH doses, which are effective and safe in non-liver disease patients, are equally so in patients with cirrhosis. In non-randomized studies [44,45], LMWH administration at a fixed dose was effective and safe in patients with established PVT. In vitro the anti-Xa assay proved suboptimal for monitoring LMWH use [46,47], while TGA was more appropriate [47]. An in vitro study also suggested that, despite of a lower anti-thrombin level, plasma from patients with cirrhosis was more responsive to LMWH than that from healthy subjects [47]. The only available randomized trial showed that LMWH at a fixed dose and without laboratory monitoring was effective and safe in preventing PVT in patients with cirrhosis [48].

Statement. ***For prophylaxis or treatment of portal vein thrombosis, low molecular weight heparin (LMWH) at fixed or weight-adjusted doses does not require laboratory monitoring (C2). In patients with cirrhosis, it is not known whether or not LMWH requires laboratory monitoring, while the anti-FXA assay does not reflect the achieved anti-coagulation with a given dosage of LMWH (C2).***

6.3. Vitamin K antagonists (VKA)

For dose-adjustment of VKA administration in non cirrhotic patients, the test to be used is the PT, with results expressed as INR (here called INR-VKA, see above for more details) and set at a therapeutic interval of 2.0–3.0 (target 2.5). Whether these same intervals apply to patients with cirrhosis has not yet been established. Regarding the APPT, the baseline PT is often prolonged in patients with cirrhosis. Thus, lower VKA doses would probably be required to achieve the optimal therapeutic interval; however, this issue has not yet been addressed. As previously mentioned, VKA are used in patients with cirrhosis; a further concern is using the INR to report the PT results. The common INR (INR-VKA) is a reliable index of the anti-coagulation level in non-liver disease patients, but may be suboptimal in patients with cirrhosis [40,41].

Statement. ***Vitamin K antagonist (VKA) should be administered to attain an INR value of 2.0-3.0 (C). However, due to the limitation of this scale in cirrhosis, the INR value might not be representative of the real anti-coagulation achieved (C2), and results may vary between centers (A). Randomized trials to assess and monitor the efficacy and safety of VKA in cirrhosis are needed.***

7. Factors tipping the hemostatic balance in cirrhosis

Factors that may impair the hemostatic balance in patients with cirrhosis are of intrinsic (i.e., liver-related) or extrinsic origin (i.e., superimposed on the liver disease).

Concerning the intrinsic factors, a pro-hemorrhagic tendency may be secondary to thrombocytopenia [49,50]. Alcohol might affect hemostasis by inducing dietary deficiencies which impair megakaryocyte maturation, inhibit platelet aggregation, and reduce global fibrinolytic capacity [51–55]. Definite evidence for impaired fibrinolysis in alcohol misusers is still needed, as previous studies assessed single components of the fibrinolytic system. In patients with primary biliary cirrhosis or sclerosing cholangitis, a hypercoagulable state has been related to hypofibrinolysis, high levels of coagulation factors and hyper homocysteinemia [56–58]. In non-alcoholic steatohepatitis, a tendency to a pro-coagulant state, characterized by increased factor VIII and reduced protein C, is common [59]. Portal hypertension, which causes thrombocytopenia, may entail a hemorrhagic diathesis. In addition, porto-systemic shunting and gut barrier disruption facilitate endotoxaemia and contribute to the hemorragic diathesis [60].

The endothelium helps to hemostasis, as VWF, t-PA and PAI-1 are derived predominantly from endothelial cells. In cirrhosis, endothelial dysfunction has been surmised by the observation of changes in levels of nitric oxide-derived by-products [61,62], flow mediated vasodilatory response of the brachial artery [63] and VWF levels [64–68]. Currently, there is no single marker that can detect endothelial dysfunction in patients with cirrhosis.

Among extrinsic factors, bacterial infections are frequent in hospitalized patients with cirrhosis, and often responsible for acute on chronic liver failure [69,70]. The condition may favor a hemorrhagic diathesis through a direct effect of bacterial products or the hyper-production of proinflammatory cytokines, causing defects in platelet aggregation [71], coagulation activation and hyperfibrinolysis [72–74], and release of endogenous heparinoids [75–77]. Deficiency in protein C activity, reported in patients with cirrhosis and severe sepsis, may precipitate disseminated intravascular coagulation [78]. Moreover, an imbalance of VWF and its cleaving protease ADAMTS13 induced by systemic inflammation was reported in cirrhosis [79]. Bacterial translocation may act either as a pro-hemostatic or an anti-hemostatic factor. Chronic endotoxin-related inflammation may raise the risk of PVT in cirrhosis [72,80]. Endotoxins favor a pro-thrombotic diathesis by increasing portal hypertension and slowing portal flow through endothelin-induced contraction of hepatic stellate cells [80], and/or by increasing the production of endothelium-associated factors [68]. In addition, endotoxemia may trigger coagulation activation [68] in patients treated with non-absorbable antibiotics, a treatment that induces a concomitant reduction in endotoxemia and thrombin generation [81,82].

Finally, patients with cirrhosis are at risk of developing both acute and chronic kidney disease [83–87]. In the general population, chronic renal disease is associated with a high thrombotic risk, while in acute renal failure the bleeding risk prevails over that of thrombosis. The hemostatic balance in patients with concomitant liver cirrhosis and acute or chronic renal disease has not been specifically investigated.

Statement. ***The etiology and severity of liver disease may alter the hemostatic balance in both directions. Endothelial dysfunction and bacterial translocation may induce a pro-thrombotic effect, while bacterial infection or sepsis may provoke a pro-hemorrhagic effect. Studies assessing the hemostatic balance in patients with cirrhosis and acute or chronic kidney disease are lacking (B).***

8. Risk of bleeding following invasive procedures or surgery

The majority of studies that assessed the risk of bleeding in relation to platelet count and/or results of coagulation tests in patients

Table 1
Post-procedural bleeding in cirrhotic patients, in relation to platelet counts and INR values.

Procedures	Study references	Bleeding following the procedure	Low platelet count ($\leq 50–60 \times 10^9$)[a]	INR > 1.5 no
Paracentesis	[19,88–91]	0.3–3%	No	No
Thoracentesis	[92,93]	2%	Unknown	Unknown
Percutaneous liver biopsy	[13,94–97]	0.5%	Yes	Likely
Transjugular liver biopsy	[98–100]	<1%	Unknown	Unknown
Dentistry	[101,102]	2.9%	No	No
Endoscopic variceal ligation	[103,104]	3–7.3%	No	No
Endoscopic polypectomy	[105,106]	3–12.4%	No	No
Percutaneous ablation HCC	[107,110]	1%	Unknown	Unknown
OLT	[28,111–114]		No	No
Liver surgery	[115]	3.9–6.6%	No	No
Cholecystectomy	[116,117]	3.9–6.6%	No	No
Hernioplasty	[118,119]	2.3–10.8%	Unknown	Unknown

[a] Definition of the low threshold value varied among studies but is usually taken as $\leq 50 \times 10^9$.

with cirrhosis undergoing invasive procedures or surgery were retrospective, and adopted a priori cut-offs for laboratory values (Table 1) [13,19,28,88–118]. In one study with a stringent inclusion criterion for platelet counts of $>50 \times 10^9$/L, a platelet count of $\leq 60 \times 10^9$/L was identified as a risk factor for bleeding after percutaneous liver biopsy [13]. Moreover, in several studies, the enrolled population consisted of patients with and without cirrhosis, and some underwent prophylactic platelets or plasma transfusions, possibly jeopardizing the interpretation of results. Lastly, for some procedures, there is no comparison with risk in patients without cirrhosis. Despite these non-negligible limitations, it appears that the bleeding rate after paracentesis, thoracentesis, and percutaneous or transjugular liver biopsy is low (<3%), and moderate (<10%) following endoscopic variceal ligation, endoscopic polypectomy, and minor abdominal surgery such as cholecystectomy or hernioplasty. In general, abnormal coagulation parameters did not predict procedure-related bleeding, while various degrees of thrombocytopenia were associated with post-procedural bleeding.

Statement. ***In patients with cirrhosis, procedure-related bleeding is uncommon (B), and standard coagulation tests are not good predictors of post-procedure bleeding. Although formal trials are lacking, thrombocytopenia (i.e., platelet count <50–60 $\times 10^9$/L) may be predictive of bleeding.***

9. Pharmacologic interventions to control or prevent bleeding

9.1. Recombinant activated factor VII

rFVIIa promotes hemostasis by binding to the surface of platelets activated at sites of vascular injury, and by directly activating factor X [24,119,120]. In patients with and without liver diseases, administration of rFVIIa shortened the abnormal PT value [119–124]. However, in randomized clinical trials rFVIIa administration to patients with cirrhosis proved ineffective in controlling bleeding from varices or bleeding during surgery [24,120,125–127].

Statements. ***rFVIIa administration shortens the prothrombin time in patients with cirrhosis. However, this laboratory effect did not translate into clinical benefits (A1).***

9.2. Platelet transfusion

In patients with cirrhosis an adequate amount of thrombin is generated in vitro when platelet counts approximate $50–60 \times 10^9$/L, optimal levels being seen with counts $>100 \times 10^9$/L [12]. However, the clinical value of these thresholds remains obscure, as at lower counts interaction of platelets with coagulation pathways is still seen in vivo. Platelet transfusion is still employed to reach such thresholds [128,129], but this practice lacks evidence-based support. Rheological studies indicated that normal platelet flow was adversely affected whenever hematocrit levels dropped to <25%, supporting the claim that this level should be maintained in patients with cirrhosis who bleed [130]. One unit of platelet concentrate ($300 \pm 30 \times 10^9$/L) for every 10 kg of body weight is usually administered, and platelet count needs to be checked after 1 h [130]. However, a correlation between improved platelet counts and enhanced hemostasis has never been shown [13]. After transfusion of one platelet unit, thrombin generation remained unaffected and ROTEM parameters did not return to normal [14].

Statement. ***Current guidelines recommend platelet transfusion when counts are <50 $\times 10^9$/L; however, this recommendation is supported only by biological plausibility (C2).***

9.3. Eltrombopag

Eltrombopag is an agonist of the thrombopoietin receptor, and its administration results in enhanced platelet production [131–135]. In HCV infected patients with thrombocytopenia, platelet numbers increased up to 100×10^9/L or more in a dose-dependent manner in 75%, 79% and 95% of patients after the use of 30, 50 and 75 mg of eltrombopag, respectively [136]. In patients with thrombocytopenia undergoing invasive procedures, eltrombopag at a dose of 75 mg daily for 14 days allowed platelet transfusion to be avoided in 72% of cases; however, six patients treated with the active drug and two with placebo experienced a thrombotic event. A post hoc analysis showed that platelet counts $\geq 200 \times 10^9$/L were associated with thrombosis [136]. Further exploration of eltrombopag therapy is warranted, including better identification of risk factors for thrombosis, dose optimization, and patient selection.

Statement. ***Eltrombopag is not indicated for reducing the units of platelet concentrates to be infused at the time of invasive procedures, as post-procedural bleeding did not differ between treated and untreated patients (A1).***

9.4. Vitamin K

Vitamin K is necessary for the carboxylation of coagulation factors II, VII, IX, and X. Intravenous injection of 10 mg daily of vitamin K for 24–48 h may restore vitamin deficiency secondary to cholestasis or malabsorption [137]. However, in patients with impaired synthetic liver function, administration of vitamin K is ineffective in normalizing PT/INR values [137–139].

Statement. ***Routine administration of vitamin K is not recommended to increase the plasma levels of coagulation factors in patients with cirrhosis, (B1).***

9.5. Fresh frozen plasma

FFP shortens an abnormal PT in various clinical conditions, including cirrhosis. However, PT (or APTT) shortening does not necessarily translate into improved bleeding control. Furthermore, the dilution of coagulation factors contained in the FFP and their relatively short half-life of 8–48 h demands large volumes to be infused [141]. Indeed, to increase the activity of coagulation factors by 1–2%, FFP needs to be infused at a dosage of 1 mL/kg body weight [142], with repeated infusions every 6–12 h [142]. These therapeutic end-points are hardly attainable in patients with cirrhosis, as large volumes of FFP may result in excessive plasma expansion and increased intracerebral pressure [143].

FFP infusion is commonly used before surgical/invasive procedures in patients with an INR ≥2 or PT prolongation >4 s [140]. Nevertheless, this practice is not evidence-based. The threshold for administering FFP was arbitrarily set at the 50% value of normal PT (i.e., INR of 2). For intracranial pressure monitoring, the threshold was raised to 80% of normal PT (i.e., an INR of approximately 1.2–1.3) [140]. During massive blood transfusion, FFP administration was advised at a ratio of 1:2 with red cells infusion, to avoid dilution of coagulation factors [144]. In patients with INR > 1.5, FFP was administered at a dosage of 12–15 mL/kg before liver biopsy, but evidence was not provided on whether or not this practice improved clinical outcomes [146]. In two studies this regimen allowed correction of PT in only 20% of patients receiving 900 mL of FFP [145,146]. The infusion of <500 mL of FFP seldom corrects the PT by more than 2–3 s [142,147]. In vitro, the addition of FFP to plasma of patients with cirrhosis proved ineffective in increasing thrombin generation [148,149]. It is important to realize that cut-off values for PT employed to trigger infusion are arbitrarily set and not based on clinical trial data. The myth of infusing FFP to treat the coagulopathy of patients with cirrhosis still dominates clinical practice, but evidence based on clinical trials is lacking.

Statement: ***Infusion of fresh frozen plasma may improve or even normalize some coagulation parameters in patients with cirrhosis, but the need to infuse high volumes makes this practice potentially unsafe (A1). The clinical benefit of infusing fresh frozen plasma in patients with cirrhosis undergoing invasive procedures lacks experimental evidence, and this practice is not routinely recommended (B2).***

9.6. Prothrombin complex concentrates

Prothrombin complex concentrates are a mixture of vitamin K dependent coagulation factors, which are present at 20-fold higher concentration than in a unit of FFP [150]. Administration of prothrombin complex concentrates improves PT in about 50% of patients with cirrhosis [145,149]. This improvement was attained at a mean dosage of 1500 mL, and associated with an increase in thrombin-antithrombin complexes, that are markers of excessive in vivo thrombin generation [149]. Thrombotic events did not occur during infusion, but other complications, including heparin-induced thrombocytopenia, were observed [151,152]. Thrombosis may be of more concern when a concomitant reduction in anticoagulant factors is common. In a single study on patients with cirrhosis, the infusion of a four factors complex concentrate allowed safe execution of interventional procedures with no complications [152]. However, the sample size of this uncontrolled study was small.

Statement: ***In patients with cirrhosis, the infusion of prothrombin complex concentrates improves PT/INR values. Further studies are needed before their use in clinical practice is recommended (C2).***

9.7. Desmopressin

Desmopressin, an analog of the antidiuretic hormone, increases plasma levels of factor VIII and VWF, probably by increasing their secretion from endothelial storage sites [153]. In patients with liver failure, its administration at a dose of 0.3 mg/kg shortened the bleeding time [154]. However, the clinical benefit of this effect remains to be verified. In a randomized trial, terlipressin was administered as monotherapy or in association with desmopressin to control variceal bleeding: no clinical benefit emerged [10]. Desmopressin failed to decrease blood transfusion requirement during hepatic resection [155]; in managing bleeding following dental extraction, the drug was not more effective than blood transfusion [156].

Statement. ***Desmopressin use is not recommended in patients with cirrhosis undergoing elective surgery or at the time of variceal bleeding (B2). Desmopressin administration in patients with cirrhosis undergoing dental extraction may be considered (B2).***

9.8. Antifibrinolytics

The use of aprotinin, a serine inhibitor which antagonizes various proteases [157], has been extensively studied in liver transplantation [158], but only one randomized trial evaluated its efficacy in 97 patients with cirrhosis: intra-operative blood loss and blood transfusion were significantly lower in the treatment group compared to placebo [159]. The efficacy of another serine protease inhibitor, nafamostat mesilate, was evaluated in 22 patients who underwent hepatic resection for hepatocellular carcinoma: despite laboratory evidence of control of hyperfibrinolysis, blood loss was not different in the treated and control groups [160]. Epsilon aminocaproic acid interferes with plasminogen binding to fibrin, thus inhibiting the conversion of plasminogen to plasmin [161]. Similarly, tranexamic acid inhibits fibrinolysis by competitively inhibiting plasminogen at 6–10-fold higher potency than epsilon aminocaproic acid [162]. In the frame of a randomized trial on 214 patients undergoing surgery, tranexamic acid administered before surgery allowed a blood transfusion-free hepatectomy [163]. In a meta-analysis of 23 studies including a total of 1407 patients with cirrhosis undergoing liver transplantation, both aprotinin and tranexamic acid reduced transfusion requirements compared to controls. No hepatic artery or venous thromboembolic events were documented following the administration of either drugs [164]. Before dental extractions, four × 100 mg mouthwashes of tranexamic acid for a week can be used to reduce bleeding [102]. Tranexamic acid has also been useful in reducing blood transfusion requirements in patients with cirrhosis and gastric antral vascular ectasia who did not respond to endoscopic treatment [165].

Statement. ***Tranexamic acid and aprotinin reduce blood loss after hepatic resection and, together with Epsilon aminocaproic acid, reduce blood loss in liver transplantation and should be recommended in hepatic surgery (A1). In patients with cirrhosis, mouth washes with tranexamic acid after dental extraction could be considered (C2), but no evidence for the efficacy of the drug in other cirrhosis conditions is available (C2).***

10. Portal and peripheral vein thrombosis

10.1. Venous thromboembolism in liver cirrhosis

Since thrombin generation in patients with cirrhosis is normal, owing to the preserved balance between pro- and anti-coagulants, the risk for VTE is not reduced as previously believed, but rather

Table 2
Incidence of VTE in patients with chronic liver disease or cirrhosis.

	Type of study	Patients, *n*	Controls, *n*	VTE cases	VTE incidence (follow up)
Garcia-Fuster, 2008 [166]	Retrospective cohort	2074 CC	–	17	0.8% (16 years)
Dabbagh, 2010 [167]	Retrospective cohort	190 CLD	–	12	6.3% (7 years)
Northup, 2006 [42]	Retrospective case–control	21,000 hospitalized CC	113 hospitalized CC without VTE	113	0.5% (8 years)
Huerta, 2007 [168]	Retrospective case–control	6550 VTE	10,000 no-VTE	–	74.5 per 100,000 person-years
Gulley, 2008 [169]	Retrospective case–control	963 CC	12,405 non-CC	18 CC 121 non-CC	1.87% (10 years)
Lizarraga, 2010 [170]	Retrospective case–control	108 CLD with VTE	Population: 14,790 CLD; Control: 108 CLD no VTE	108	0.73% (4 years)

CC: patients with cirrhosis; CLD: chronic liver disease; VTE: venous thromboembolism.

Table 3
Prevalence of VTE in patients with chronic liver disease or cirrhosis.

	Type of study	Patients, *n*	Controls	VTE cases	VTE prevalence
Aldawood, 2011 [171]	Retrospective cohort	226 CC	–	6	2.7%
Lesmana, 2010 [172]	Retrospective case–control	12 CC with VTE	244 CC without VTE	12	4.7%
Walsh, 2013 [173]	Retrospective case–control	27 CLD with VTE	81 CLD without VTE	17	0.65%
Wu, 2011 [174]	Population based retrospective case–control	408,253 C-CC 241,626 D-CC	575,057 hospitalized non CC	3307; 1981; 4370	0.81% C-CC; 0.82% D-CC; 0.76% controls
Saleh, 2011 [175]	Population based retrospective cohort	4,927,000 AlcCLD 4,565,000 nAlcCLD	–	Alc CLD 30,000; nAlcCLD 42,000	0.6% AlcCLD 0.9% nAlcCLD
Ali, 2011 [176]	Population based retrospective cohort	449,798 CC	–	8321	1.8%

AlcCLD: Alcoholic Chronic Liver Disease; CC: patients with cirrhosis; D-CC: decompensated patients with cirrhosis; nAlcCLD: non-Alcoholic Chronic Liver Disease; VTE: venous thromboembolism.

increased due to immobilization, surgery, concomitant diseases such as cancer and endothelial dysfunction. Estimates of VTE in patients with cirrhosis are discordant [42,43,166–176], due to retrospective collection of data, high heterogeneity of patients' characteristics, and study design. Reported rates range from 0.5% to 6.7% for incidence (Table 2), and from 0.6% to 4.7% for prevalence (Table 3), with higher values in patients with more severe liver disease [173] and in those with hepatocellular carcinoma [176]. Prophylaxis for VTE with anti-coagulants in patients with cirrhosis was shown to be safe and effective [177,178].

Statement. ***Patients with cirrhosis are not protected against VTE and should not be precluded from receiving antithrombotic prophylaxis in conditions with increased risk for VTE (C2).***

10.2. Portal vein thrombosis in cirrhosis

PVT is frequent in cirrhosis [35,48,179–190], with a 1-year incidence of 4.6–16.7% (Table 4), and prevalence of 1.4–26.1% (Table 5). Prevalence increases with the severity of cirrhosis [186,190], with rates of up to 44.4% in patients with hepatocellular carcinoma.

Slow portal blood flow, vessel wall damage and hypercoagulability are risk factors for PVT in patients with cirrhosis [191–193]. Other risk factors include male sex, previous abdominal surgery, encephalopathy, ascites, a low platelet count and a history of bleeding varices [35,184,194–198]. The role of inherited or acquired thrombophilia, as well as of previous sclerotherapy for variceal bleeding, is uncertain [35,184,194–198].

Doppler ultrasound is accurate for diagnosing thrombosis of the main portal vein and its intrahepatic branches, but false negative results may occur in cases with limited occlusion [199–201]. Multiphasic helical CT or MRI are recommended to confirm the finding and evaluate patency of the superior mesenteric vein (SMV), splenic veins, or the occurrence of portosystemic shunts. Classification of PVT is important for medical treatment and surgery and the Yerdel's classification which grades the length of portal vein involvement and its extension seems adequate [202]. PVT is classified as grade 1 when <50% of the lumen is occluded with no or minimal extension to SMV; grade 2 when >50% of the portal vein is occluded; grade 3, when the portal veins and proximal SMV are occluded; grade 4 when the portal vein and SMV thromboses extend to their distal portions.

Statement. ***In patients with cirrhosis a Doppler ultrasound at 6-month intervals should be implemented as a screening procedure for the detection of portal vein thrombosis (C1). Whenever thrombosis is encountered, CT scan/MRI are recommended to evaluate its extension, adopting the Yerdel's classification (B1).***

10.3. Impact of portal vein thrombosis on the natural history of cirrhosis

The influence of PVT on the natural history of cirrhosis is debated. Partial PVT may progress to complete occlusion and/or extend to other splanchnic vessels in 40–70% of cases; conversely, spontaneous recanalization of occluded veins may occur [203,204].

Table 4
Incidence of portal vein thrombosis (PVT) in cirrhosis of different etiology without hepatocellular carcinoma.

	Type of study	Study period	Number of patients	Incidence of PVT	
				n	%
Zocco, 2009 [179]	Prospective cohort	Not specified	73	12	16.4
Villa, 2012 [48]	Prospective case–control	2008–2010	36	6	16.7
Maruyama, 2013 [180]	Retrospective case–control	1998–2009	148	19	12.8
John, 2013 [181]	Prospective cohort	2004–2009	243	–	8.4
Nery, 2015 [182]	Prospective case–control	2000–2009	1243	–	4.6

Table 5
Prevalence of portal vein thrombosis in cirrhosis of different etiology without hepatocellular carcinoma.

First author, year, reference	Type of study	Study period	Number of patients	Prevalence of PVT	
				n	%
Violi, 1994 [6]	Prospective case–control	1990–1991	73	9	12.3
Amitrano, 2000 [35]	Prospective case–control	1998–1999	328	26	7.9
Amitrano, 2004 [184]	Prospective case–control	1998–2002	701	79	11.3
Robles, 2004 [185]	Prospective cohort	1988–2001	455	32	7.0
Fimognari, 2005 [186]	Prospective case–control	Not specified	136	33	24.1
Lendoire, 2007 [187]	Retrospective case–control	2005–2006	299	26	8.7
Weber, 2009 [188]	Retrospective case–control	1998–2006	88	23	26.1
John, 2013 [181]	Prospective cohort	2004–2009	290	70	24.1
Girleanu, 2014 [189]	Prospective cohort	2011	1580	22	1.4
Berry, 2014 [190]	Retrospective cohort	2002–2013	66,506	2207	3.3
Nery, 2015 [182]	Prospective case–control	2000–2006	1278	35	2.7

The impact of PVT on patients' outcome was prospectively evaluated in two studies [180,182]. In the Maruyama et al. study, occurrence of PVT, partial in most cases, affected neither the incidence of variceal bleeding nor patient' survival. In the Nery et al. study, PVT correlated with the severity of portal hypertension, but was not responsible for further liver impairment. In these patients, the rate of spontaneous recanalization of portal veins was exceptionally high (70%), compared with only 1/41 in the prospective study by Luca et al. [202]. Retrospective studies [43,181,203,205] yielded discordant data but overall indicated poorer survival in patients with stable or progressive PVT, if left untreated [2,4,5]. In addition, PVT in liver transplant candidates correlated with increased mortality after liver transplantation [206].

Statement. ***Complete or partial portal vein thrombosis (PVT) with extension to the superior mesenteric vein increases mortality in liver transplant candidates and in patients with variceal bleeding (B2). Monitoring of patients with isolated PVT by Doppler ultrasound is recommended, as the occlusion may extend in some patients and regress in others (B2).***

10.4. Anti-coagulation for the prevention/treatment of portal vein thrombosis

The value of preventing PVT by the administration of anti-coagulants in patients with cirrhosis has been established: in a controlled trial a 12-month course of enoxaparin was safe; in addition, no bleeding occurred in treated or untreated patients [48]. Although encouraging, these preliminary results need confirmation in further studies. The safety of longer regimens and in patients with more advanced cirrhosis, excluded from the cited trial, warrants further investigation.

Regarding the efficacy and safety of anti-coagulant therapy in patients with cirrhosis and established PVT, available data consist of 5 case series with a total of 163 subjects [204,207–210]: at month 6 of therapy, complete or partial recanalization occurred in 33–45% of patients, while extension of the thrombus was observed in <10%. Factors predicting recanalization were recent onset (<6 months) of the thrombus and partial PVT [211–213]. Treatment prolongation resulted in higher rates of recanalization and a lower likelihood of extension. Although the majority of treated patients recalled a past variceal bleeding or high-risk varices, a bleeding event was recorded in only 5%. After anti-coagulation is stopped, the benefit wanes rapidly, as PVT recurred in 40% of patients.

There is no agreement on which anti-coagulant should be administered, as LMWH or VKAs have their own advantages and disadvantages. LMWH is as safe and effective as VKAs, but less practical because of the need for subcutaneous injections. LMWH does not interfere with the MELD score and may be used until transplantation. A platelet count $<50 \times 10^9$/L and the use of VKA were the only factors more frequently observed in patients with bleeding related to anti-coagulation therapy [207]. Direct oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban and edoxaban) are now available as substitutes for VKA in non-liver disease patients, but their effectiveness/safety in patients with chronic liver disease remains to be assessed.

Statement. ***Before starting anti-coagulation it is advisable to check for the presence of varices, initiate beta blockers treatment, or perform rubber band ligation in patients with large varices or in those with previous variceal bleeding (C2). Thrombosis prophylaxis should not be withheld from patients with cirrhosis (B2). In patients with cirrhosis and portal vein thrombosis, anti-coagulation is safe and effective (B1). Prophylactic or elective treatment should be attempted by low molecular weight heparin (LMWH) or vitamin K antagonist (VKAs). In patients with platelet counts $<50 \times 10^9$/L, LMWH could be the best choice (C2). In candidates for liver transplantation, anti-coagulation should be maintained until transplantation (2B). Whether or not long-term anti-coagulation should be maintained in patients with cirrhosis ineligible to transplantation remains to be established.***

Conflict of interest
None declared.

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Appendix B. Participants involved in the review

Participants involved in the review of published evidence, and formulation of the proposed consensus statements, all of whom should be considered as co-authors of the present report.

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Appendix C. Voting jury

Chairmen: Roberto de Franchis (Milan, Italy), Pier Mannuccio Mannucci (Milan, Italy).

Members: Calogero Cammà (Palermo, Italy), Umberto Cillo (Padua, Italy), Alfredo Di Leo (Bari, Italy), Stefano Fagiuoli (Bergamo, Italy), Ivan Gardini (Vimercate, Italy), Angelo Gatta (Padua, Italy), Giacomo Laffi (Florence, Italy), Tecla Mastronuzzi (Bari, Italy), Renzo Pegoraro (Padua, Italy), Domenico Prisco (Florence, Italy), Francesco Salerno (Milan, Italy), Paolo Simioni (Padua, Italy).

Appendix D. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2016.02.008.

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