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Hemostasis in Liver Disease: Implications of New Concepts for Perioperative Management

Pepijn D. Weeder [a,b], Robert J. Porte [a], Ton Lisman [b,*]

[a] Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[b] Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

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ABSTRACT

The hemostatic profile of patients with liver diseases is frequently profoundly different from that of healthy individuals. These complex alterations lead to abnormal results from routine laboratory tests, but because of the nature of these assays, they fail to accurately represent the patient's hemostatic state. Nevertheless, based on abnormal laboratory coagulation values, it has long been assumed that patients with liver disease have a natural bleeding tendency and are protected from thrombosis. This assumption is false; the average patient with liver disease is actually in a state of "rebalanced hemostasis" that can relatively easily be tipped toward both bleeding and thrombosis. The new paradigm of rebalanced hemostasis has strong implications for the clinic, which are presented in this review. There is no evidence that prophylactic transfusion of plasma helps to prevent procedure-related bleeding. In addition, the presence of independent risk factors such as poor kidney status or infections should be carefully assessed before invasive procedures. Furthermore, central venous pressure plays an important role in the risk of bleeding in patients with liver diseases, so during procedures, a restrictive infusion policy should be applied. Finally, thrombosis prophylaxis should not be withheld from patients with cirrhosis or acute liver failure, and clinicians should be alert to the possibility of thrombosis occurring in these patients.

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Chronic liver disease and acute liver failure are associated with considerable changes of the hemostatic profile [1]. Historically, these changes were interpreted as predisposing for a bleeding tendency, and patients often received prophylactic transfusion of blood products prior to invasive procedures with the aim of reducing the bleeding risk. Developments in the care of liver transplant recipients, combined with experimental laboratory studies, have introduced new concepts with regard to the management of hemostatis in patients with chronic and acute liver disease. In brief, routine laboratory coagulation tests cannot predict bleeding risk, and prophylactic use of blood products

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* Corresponding author at: Ton Lisman, PhD, Department of Surgery, BA33, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.
E-mail addresses: p.d.weeder@umcg.nl (P.D. Weeder), r.j.porte@umcg.nl (R.J. Porte), J.A.lisman@umcg.nl, tonlisman@hotmail.com (T. Lisman).

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may paradoxically contribute to bleeding rather than prevent it. These new insights have brought about a reduction in the use of blood products in patients undergoing liver transplantation. More and more centers report transfusion-free liver transplantation in a substantial proportion of patients [2]. These developments have profound implications for the general treatment policy for patients with liver disease who need to undergo an invasive procedure. Although avoidance of correction of the laboratory coagulopathy prior to surgery has been established in liver transplantation practice, the old dogma of prophylactic blood product transfusion guided by laboratory testing prior to other, less major invasive procedures still prevails [3,4]. This article reviews the developments in liver transplant surgery with regard to the management of hemostasis in patients with liver disease. In addition, we provide guidelines for the application of these newer insights in the management of hemostasis in patients with liver disease undergoing other invasive procedures.

The Hemostatic Profile of Patients With Liver Disease

The liver plays a central role in hemostasis as it synthesizes nearly all circulating coagulation factors and inhibitors, as well as some of the components of the fibrinolytic system. In addition, the liver synthesizes thrombopoeitin, which is a hormone essential for stimulation of platelet production from megakaryocytes in the bone marrow. Therefore, liver diseases (whether acute or chronic) frequently are associated with complex alterations of the hemostatic system. The typical hemostatic profile of patients with advanced liver disease consists of significantly decreased levels of nearly all proteins that promote or inhibit coagulation and fibrinolysis, thrombocytopenia, and platelet function defects. The reduced plasma levels of coagulation proteins can be directly explained from the loss of function of the failing liver but may also be a reflection of ongoing low-grade intravascular or intrahepatic activation of coagulation [5–7]. In contrast to most hemostatic proteins, levels of von Willebrand factor (VWF) are elevated, which could be due to enhanced production by the endothelium or reduced clearance by the liver. These elevated VWF levels may also be part of a compensatory mechanism that aids primary hemostasis [8]. Plasma levels of factor VIII are also substantially increased, which could be explained by physiological synthesis in other organs, which may be up-regulated in patients with liver failure [9,10]. The increased levels of factor VIII may be related to the elevation of its carrier protein VWF. Many patients with chronic liver diseases have portal hypertension and splenomegaly, which respectively leads to alterations in hemodynamics and increased platelet sequestration [11,12]. Results from routine laboratory tests like the prothrombin time (PT), its standardized variant international normalized ratio (INR), and activated partial thromboplastin time (APTT) are frequently prolonged [13]. In addition, patients with cirrhosis may have laboratory features of accelerated fibrinolysis, although this is debated [14,15]. In contrast, patients with acute liver failure present with laboratory features of inhibited fibrinolysis [16].

Although different etiologies of liver failure share the same general hemostatic pattern, there are notable differences between different types of liver disease. In cholestatic liver diseases, including primary sclerosing cholangitis and primary biliary cirrhosis, the hemostatic changes seem to be less pronounced as compared with patients with parenchymal disease [17,18]. In addition, patients with nonalcoholic fatty liver disease, a disorder with increasing prevalence in conjunction with the rise of obesity prevalence [19,20], are relatively prothrombotic reflected in the high incidence of thrombosis [21,22]. In patients with acute liver failure, thrombocytopenia is less common than chronic liver disease. The decrease in procoagulant and anticoagulant plasma factors, however, is generally more pronounced in acute than in chronic liver failure [21,23], and the average INR is higher [24].

Rebalanced Hemostasis

The classical interpretation of the hemostatic profile in patients with liver disease was that these patients have a bleeding tendency. This was believed to be supported by the abnormal laboratory coagulation test results and the observation that spontaneous bleeding occurs frequently in this group of patients. Furthermore, the fact that liver transplant recipients frequently required massive amounts of blood products during the procedure was also considered evidence of an existing bleeding tendency. This led to the clinical practice of preprocedural prophylactic correction of the platelet count, PT, and APTT through transfusion of blood components, with the assumption that this would help prevent intraoperative bleeding [3,4]. The types of transfusions that are frequently used include fresh-frozen plasma, platelet concentrates, cryoprecipate (or fibrinogen concentrate), packed red blood cell (RBCs), and/or whole blood. In line with this paradigm, patients were considered to be "auto-anticoagulated" and thromboprophylaxis was frequently withheld.

After several authors had pointed out the shortcomings of this classical interpretation of the coagulopathy of liver disease [5,6,25,26], we proposed the concept of "rebalanced hemostasis" [27]. In healthy individuals, hemostasis is in a solid balance between procoagulant and anticoagulant factors, thereby preventing bleeding or thrombosis. Both procoagulant and anticoagulant drivers are lowered in patients with liver disease, or compensatory mechanisms for hemostatic defects exist. Specifically, thrombocytopenia and platelet function defects are compensated (at least in part) by elevated levels of VWF, and coagulation and fibrinolysis are in a rebalanced status because of a concomitant decline in activators and inhibitors [27]. This rebalanced status is not reflected by the routinely performed hemostatic tests (platelet count, PT, APTT). Because the platelet count does not take the elevated VWF levels into account and because the PT and APTT are only sensitive for procoagulant proteins, they fail to reflect the polyfactorial changes in the hemostatic profile of patients with liver disease. Although spontaneous bleeding frequently occurs in patients with liver disease, in most cases, these are variceal bleedings that are caused by local vascular deformations and hemodynamic changes rather than coagulopathy. Furthermore, thrombotic complications also frequently occur in patients with liver disease (see later section for details), which would be unlikely, if not impossible, if patients were really "auto-anticoagulated." Finally, in the present-day practice of liver transplantation, a large proportion of patients are successfully operated on without the need of any blood transfusion [2,28]. If liver disease caused "true" coagulopathy, as observed in conditions such as hemophilia, this would likely not be possible [21].

The Limitations of PT and APTT and the Potential of Thrombin Generation Assays

The PT has been developed as a tool to diagnose defects or deficiencies in individual procoagulant proteins and to evaluate patients using vitamin K antagonist therapy [26]. However, the PT has been adopted as a general indicator of coagulation in a broad range of patients. Because of the nature of the assays, the PT and APTT cannot predict the risk of bleeding in patients with complex hemostatic alterations such as observed in liver disease [26,29–32]. The main reason for this is that these tests are insensitive to plasma levels of the anticoagulant pillars of hemostasis, that is, the protein C pathway, antithrombin, and tissue factor pathway inhibitor. In addition, these tests do not take the role of the endothelium in the hemostatic process into account. The PT only assays the function of a discrete number of procoagulant proteins (factors VII, X, V, and II and fibrinogen) and therefore cannot reflect the true hemostatic status of a patient.

In recent years, the thrombin generation test, which may more accurately reflect the status of the hemostatic system, has gained interest. In this test, the total amount of thrombin generated during in vitro coagulation is measured, which contrasts with the PT and APTT,

which measure the time it takes to form a plasma clot. Notably, when a clot is formed, only ~5% of the total thrombin has been generated. The thrombin generation test has been modified by addition of thrombomodulin, an endothelial receptor required for activation of the endogenous anticoagulant protein C system. This modified thrombin generation test is sensitive to all anticoagulant drivers in plasma. It has been shown that despite a prolonged PT and APTT, patients with stable cirrhosis or patients undergoing liver transplantation can still generate thrombin at a normal to increased rate [33,13]. In acute liver failure, the PT and APTT are more severely affected, but this is not associated with lower thrombin generation [16,34] or an increased risk of bleeding [24,35,36]. Although the thrombin generation test appears to more accurately estimate the hemostatic potential in plasma, it is unclear whether the test is useful in predicting bleeding or thrombosis. In addition, the assay is not widely available and, at present, too complex for use in routine diagnostic laboratories.

Whole blood thromboelastography is another technique that may be helpful in the management of hemostasis in patients with liver disease [37,38]. It works by measuring the force that is exerted on a small metal rod that is suspended in whole blood during clot formation while either the rod or container is being rotated [38]. Because the assay quantifies multiple aspects of clot formation over time, it can be used to identify specific coagulopathies such as hyperfibrinolysis [39]. There are 2 commercially available point-of-care devices (Thromboelastography (TEG), Haemonetics corp., Braintree, MA and Rotational thomboelastometry (ROTEM), Tem International GmbH, Munich, Germany) that have been routinely used to assess hemostasis and guide transfusion during liver transplantation [37,39]. TEG- or ROTEM-guided transfusion in actively bleeding patients without liver disease was shown to reduce the amount of bleeding but has no clear effect on mortality [40]. In addition, hypercoagulability as measured by TEG predicts the risk of postoperative thrombosis [41]. Unfortunately, to date, no studies have directly tested whether TEG, ROTEM, or other global tests such as thrombin generation testing are useful in predicting procedural bleeding risk in patients with liver disease [38]. Such studies are urgently required to further improve procedural hemostatic management in these patients. TEG- or ROTEM-based studies are preferred above thrombin generation–based studies given the complexity of the latter assay.

Bleeding Does Occur Frequently But Is Mostly of Hemodynamic Origin

Bleeding from esophageal varices occurs in 25% to 35% of patients with cirrhosis and accounts for 80% to 90% of bleeding episodes in these patients [42]. It has now been widely accepted that the presence and rupture of varices is a consequence of portal hypertension and local vascular abnormalities with a (at most) minor role for hemostasis [43]. It has been shown that central venous pressure (CVP) and the splanchnic venous pressure are key factors in the hemostatic balance during liver surgery [44,45], a fact that is supported by the finding that maintaining a low CVP intraoperatively significantly reduces blood loss and the need for transfusion during liver transplantation and liver resection [44–47]. In acute liver failure, a disorder in which portal hypertension and esophagial varices are uncommon, spontaneous bleeding is rare. Also, the occurrence of bleeding complications during or after the placement of intracranial pressure monitors is infrequent [24,48]. The risk for spontaneous intracranial bleeding is very low and equal to that of control subjects [49]. Considering the importance of pressure for bleeding risk, the prophylactic administration of blood components in patients without clinically significant hemorrhage may paradoxically cause bleeding because of volume overload and further increase of the pressure in the central venous system.

There are several other independent factors that can contribute to a bleeding tendency. Well-characterized factors are the renal status [50,51] and bacterial infection [52–54]. In addition, body temperature, ionized calcium, and the acid-base balance are important in procedural bleeding [55]. The management of these factors will be discussed in the second half of this review.

Thrombosis Occurs Frequently and Might Be Underreported

As mentioned before, it has long been incorrectly assumed that patients with liver disease are auto-anticoagulated and therefore protected against thrombotic complications [25,56,57]. However, portal vein thrombosis (PVT) is a common complication in patients with cirrhosis that is encountered in 8% to 26% of patients who are candidate for liver transplantation [58–61] as compared with a lifetime cumulative incidence of 1% in the general population [62]. The reduced portal blood flow and blood vessel damage may play an important role in the increased risk of PVT [27,59], but the hemostatic status may also contribute because patients with cirrhosis carrying the prothrombin G20210A mutation appear to have an increased risk for PVT [63,64]. In addition, multiple studies have shown that venous thrombosis is not uncommon in patients with liver disease, and some studies even suggested that the risk of venous thrombosis is significantly higher in patients with liver disease as compared with individuals without liver disease [56]. It is conceivable that the incidence of thrombosis in liver disease may be underreported because symptoms of deep vein thrombosis or pulmonary embolism are nonspecific and clinicians may be less attentive to the possibility of thrombosis in this group of (critically ill) patients.

Although the reported clinical experience is limited, anticoagulant treatment of patients with liver disease with low-molecular-weight heparin (LMWH) appears safe [65]. Therefore, LMWH administration for the prevention of deep venous thrombosis should not be withheld from patients with cirrhosis and abnormal coagulation test results, although the efficacy of thromboprophylaxis in patients with cirrhosis remains unclear [66]. Low-molecular-weight heparin has also shown to be safe and effective in the prevention of PVT [67], and the pharmacologic modulation of coagulation may even have beneficial effects on the progression of cirrhosis [67–70]. Also, LMWH is relatively safe for the treatment of existing deep venous thrombosis and PVT and results in recanalization in a large proportion of patients [71,72].

Blood Transfusion Is Potentially Harmful and May Not Help in Preventing Bleeding

Blood (product) transfusion is associated with the risk of adverse effects and may be a risk factor for increased mortality [73–77]. A recent randomized controlled trial showed that the use of a restrictive RBC transfusion policy in patients with acute upper gastrointestinal bleeding (a common complication of cirrhosis) improves survival and reduces rebleeding risk, by mechanisms related to decreased administration of volume as well as direct adverse effects of RBCs [78]. Adverse effects include transfusion-related acute lung injury [79–81], hemolytic reactions, graft-vs-host disease, transfusion-related sepsis, and transmission of infectious diseases [73,82]. Because of these hazards, reduction of the use of blood products should be a goal in itself. In addition, there is no evidence for a beneficial effect of fresh-frozen plasma or platelet concentrates in preventing bleeding, but there are large studies that show that they do not [83,84]. Recently, experts recommended against prophylactic transfusion of plasma to prevent bleeding in patients with liver diseases [24,35]. A clinical trial in which a thrombopoeitin receptor agonist (eltrombopag) was administered to patients with cirrhosis to increase the platelet count prior to invasive procedures was prematurely terminated because of thrombotic complications [85]. The excess thromboses in patients receiving eltrombopag may have been related to the elevated levels of VWF in these patients in combination with a normalized platelet count [86].

This suggests that it is very unlikely that directed correction of thrombocytopenia in these patients is helpful.

Considering that (i) patients with liver disease are in a rebalanced hemostatic state [27]; (ii) the PT and APTT do not predict the risk of bleeding; (iii) evidence that prophylactic transfusion helps to prevent bleeding is lacking; and (iv) complete correction of the PT and APTT is almost never achieved, prophylactic treatment with plasma should not be applied routinely. Because highly elevated levels of VWF balance thrombocytopenia in patients with liver diseases, prophylactic platelet transfusions should also not be administered on a routine basis. Furthermore, the volume load associated with transfusion may aggravate bleeding risk rather than diminish it [44]. In case of acute liver failure, the PT and APTT also lose their value as parameters of liver function when patients receive plasma transfusion. Because the PT-INR is an important prognostic parameter in patients with acute liver failure [35], plasma transfusions should be avoided whenever possible. Nevertheless, the preventive treatment with large amounts of blood components is still common practice for both patients with cirrhosis or acute liver failure [4,48,84].

Treatment Guidelines

The narrative outlined to this point largely originates from the field of liver transplantation, in which it is in many centers a common practice not to administer any blood products prior to or during the procedure unless active bleeding occurs [2,28,39,55,76,87,88]. It is reasonable to assume that this restrictive transfusion policy is also valid for smaller invasive procedures performed on patients with liver disease. Surprisingly, prophylactic transfusions are frequently routinely administered prior to smaller invasive procedures. Societal guidelines describe conflicting policies toward transfusion. For example, the American Association for the Study of Liver Diseases (AASLD) guidelines for liver biopsy carefully argue against prophylactic transfusion [89], whereas the Society of Interventional Radiology guidelines advise to correct an INR greater than 1.5 and a platelet count less than 50 000/μL [90]. Considering the extent of the surgical trauma and the duration of the procedure, it is hard to imagine a greater hemostatic challenge for the patient than liver transplantation. We therefore suggest to abandon the old practice of PT- and platelet count–guided prophylactic transfusion and to adopt the following guidelines that are now increasingly accepted in liver transplantation care (Fig.).

Prevention and Treatment of Bleeding

Watchful Waiting

Given the aforementioned considerations, we believe that a policy of watchful waiting is most likely superior to preventive correction of laboratory tests, as evidenced by the experience in liver transplantation, although admittedly both strategies have not yet been compared in randomized studies with clinically relevant end points. Because the laboratory testing available at this time cannot predict the risk of bleeding, the best option is to treat only those patients with significant *hemostatic*, to be distinguished from surgical, bleeding. Clinically, a bleeding complication during surgery that is likely attributable to inadequate hemostatic capacity is characterized by multiple simultaneous bleeding sites, persistent oozing from a nonidentifiable source, or delayed bleeding after adequate hemostasis; a single site of bleeding, especially if in the operative area, strongly suggests a local (surgical) problem. The platelet count, PT, APTT, and fibrinogen level may be useful in guiding the transfusion in actively bleeding patients. Furthermore, more global techniques based on whole blood, such as thromboelastography (TEG or ROTEM), may be used to assess the hemostatic status intraoperatively [91].

Splanchnic Pressure, Portal Pressure, and CVP

Patients with portal hypertension have a relative pooling of blood on the venous side of the circulation and arterial hypotension. Additional fluid that is introduced into the circulation adds up to the venous overload. An important strategy to prevent bleeding during invasive procedures is to maintain a low splanchnic and portal pressure and a low total circulating volume intraoperatively. Because portal pressure cannot be reliably measured directly, CVP is generally used as a parameter [44]. Low CVP can be achieved by a restrictive infusion policy and forced diuresis. This strategy has been shown to considerably reduce perioperative blood loss during liver resection and liver transplant surgery [44,45]. It is, however, of key importance to maintain sufficient tissue perfusion, especially of the kidneys. This can be accomplished through the use of vasoconstrictors. The groups of Massicotte et al [47,92] and Hashimoto et al [93] have even applied preoperative phlebotomy to reduce the total circulating volume during transplantation or liver resection, respectively. Massicotte et al [2] have recently reported results of 500 consecutive transplants in which 79% of patients did not receive any transfusion. Although studies agree that a low CVP reduces perioperative bleeding, there is some debate whether it has a negative effect on kidney function [46,94]. In the study of Massicotte et al, no negative outcome on kidney function was found. In a randomized controlled trial comparing the use of low and normal CVP during liver transplantation, a significant reduction of blood loss was achieved with no effect on kidney function [46]. This suggests that the application of low CVP is a safe method to reduce bleeding.

Other Factors Influencing the Risk and Treatment of Bleeding

Beyond CVP, other factors that impact the risk of bleeding have been identified. Firstly, it is important to remember that the hemostatic

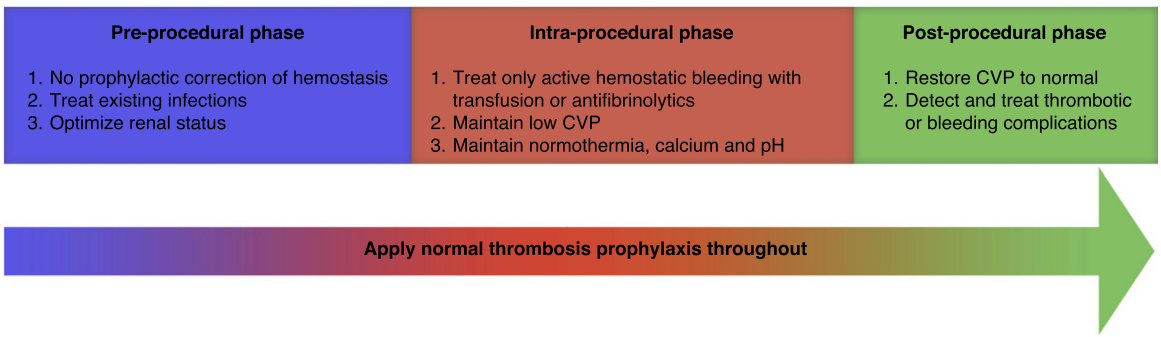

Fig. Guidelines for the hemostatic management of patients with liver disease undergoing invasive procedures.

balance may be variable depending on the degree and underlying cause of liver disease. Moreover, the existence of bacterial infection increases the risk of and failure to control bleeding [52–54]. Furthermore, the prophylactic administration of antibiotics to patients with cirrhosis is known to reduce mortality and improve hemostatic function, but the exact mechanism is unknown. The adequate surveillance for and treatment of infections before invasive procedures is therefore recommended. In addition, kidney status also predicts bleeding risk [50,51]. The effects of kidney failure on hemostasis are multidimensional, but one mechanism that plays a role is that uremia impairs platelet function [95]. In addition, RBCs are important in clot formation, and kidney failure is also often accompanied by anemia [96]. Red blood cell transfusion with the aim of preventing bleeding is, however, not indicated, as this has not been shown to reduce bleeding risk. Finally, to reduce procedural bleeding risk, the anesthesiologist should guard normothermia, free ionized calcium, and the acid-base balance closely. Plasma and RBCs contain citrate, which cause hypocalcemia. Free ionized calcium should therefore be measured regularly and corrected to at least 1 mmol/L to prevent disorders of hemostasis [97]. In vitro evidence shows that acidosis impairs clot formation and reduces clot strength when measured with TEG [98].

The prophylactic use of antifibrinolytics has been shown to reduce blood loss and transfusion requirements during liver transplantation [99]. Aprotinin has been extensively studied and used in the past [104] but was retracted from the market as a result of adverse effects reported in cardiac surgery [105]. The currently ongoing HALT-IT trial (www.clinicaltrials.gov, identifier: NCT01658124) is assessing antifibrinolytics for the prevention of gastrointestinal bleeding. Fibrinogen concentrate or cryoprecipitate may be applied to treat active bleeding in patients with low (<1 g/L) fibrinogen plasma levels [100–102]. Guidance with TEG may be useful in this context. Administration of low-volume prohemostatics, such as prothrombin complex concentrates, may be preferred over plasma because the latter results in exacerbation of portal hypertension and potentially increases bleeding risk. The effect of prothrombin complex concentrates on the prevention of bleeding during liver transplantation is currently being investigated in a multicenter randomized controlled trial [103].

Prevention and Treatment of Thrombosis

Because liver disease does not protect against thrombosis, thrombosis prevention schemes related to immobilization or invasive procedures should not be withheld from these patients [106]. Although there is accumulating experience with the use of LMWH, the use of these drugs is complicated because of serious dosing and monitoring [107] issues as a result of the abnormal hemostatic profile in patients with liver disease [108,109]. Specifically, the anticoagulant potency of LMWH appears to be increased in patients with liver disease as compared with patients with intact liver function [110]. At the same time, the anti-Xa assay underestimates the true LMWH mass in patients, which would lead to potentially dangerous dose escalations [110,111]. The limited data available suggest that treatment with vitamin K antagonists has an unacceptably high bleeding risk [57,112]. However, because these drugs are monitored by the INR, which is already prolonged in many patients with liver disease, the optimal target range is unclear, and it may be that dosing regimens were too vigorous in published series [57,112,113]. Prevention and treatment decisions are further complicated by the heterogeneity of the hemostatic profile between cases and within patients over time. Clinicians should be aware of the possibility of thrombosis and treat those patients with liver disease that are affected by it. Unfortunately, no evidence-based guidelines or target ranges for the various anticoagulant drugs for prevention and treatment of thrombosis in patients with liver disease are presently available [58]. In patients who are operated on under low CVP, physiological blood pressure must be restored postoperatively because low flow of blood is a risk factor for thrombosis (Virchow triad).

Conclusion

It has been well established that the average patient with liver failure is in hemostatic balance and may experience both bleeding and thrombotic events. The platelet count, PT, and APTT are poor predictors of bleeding risk and the prophylactic correction of these parameters with platelet concentrates or plasma does not reduce bleeding. Furthermore, the use of blood products has severe adverse effects and may cause bleeding by increasing volume load.

These insights should be put to practice in all interventions on patients with liver disease. They only need to be treated for coagulopathy when experiencing active bleeding of hemostatic origin. Moreover, CVP and total circulating volume should be kept low intraoperatively, and risk factors for bleeding such as infection and renal failure should preferably be addressed prior to surgery. Thrombosis prophylaxis should not be withheld from these patients, although specific guidelines for dosing and monitoring are lacking. Physicians from all disciplines dealing with patients with liver disease who require invasive procedures should implement the new knowledge presented in this review in their standard of practice.

The concept of rebalanced hemostasis in patients with liver disease is affirmed by the reported experience in liver transplantation. Although it is clear that the old treatment paradigm of prophylactic correction of abnormal hemostatic parameters should be abandoned, specific data to support treatment schemes based on this new approach are scarce. There are reports of high variability in transfusion rates between individual anaesthesiologists and different centers [114,115], which is likely due to a lack of specific protocols. Moreover, the specifics on how to achieve low CVP without risking hypoperfusion are subject to local interpretation and experience. Also, reference values and monitoring tools for the use of LMWH are lacking.

Patients with cirrhosis and acute liver failure are a heterogenous group. Although these patients are better off as a group when treated according to the guidelines described in this article, it is possible that a true coagulopathy does exist in a specific subset of them. Because of the lack of a clinically applicable coagulation test that reliably predicts the risk of bleeding, clinicians currently cannot identify individual patients with an increased bleeding risk, apart from the risk factors mentioned in this article. It should therefore be a priority to focus research effort on developing a method that can accurately predict bleeding risk in patients with liver disease. Future research should also focus on the performance of anticoagulation therapies for the prevention and treatment of thrombosis in this group of patients. Finally, if modern hemostatic management for all invasive procedures performed on patients with liver diseases is implemented in the context of randomized controlled trials, this could yield valuable data that are currently limited.

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