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Published in:
Minerva anestesiologica

DOI:
10.23736/S0375-9393.19.13468-2

Publication date:
2019

Online version at http://www.minervamedica.it

Minerva Anestesiologica 2019 July;85(7):782-98
DOI: 10.23736/S0375-9393.19.13468-2

EXPERTS' OPINION

Perioperative hemostatic management in the cirrhotic patient: a position paper on behalf of the Liver Intensive Care Group of Europe (LICAGE)

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ABSTRACT

Recent data demonstrated that amongst patients undergoing elective surgery the prevalence of cirrhosis is 0.8% equating to approximately 25 million cirrhotic patients undergoing surgery each year worldwide. Overall, the presence of cirrhosis is independently associated with 47% increased risk of postoperative complications and over two and a half-increased risk of in-hospital mortality in patients undergoing elective surgery. In particular, perioperative patients with chronic liver disease have long been assumed to have a major bleeding risk on the basis of abnormal results for standard tests of hemostasis. However, recent evidence outlined significant changes to traditional knowledge and beliefs and, nowadays, with more sophisticated laboratory tests, it has been shown that patients with chronic liver disease may be in hemostatic balance as a result of concomitant changes in both pro- and antihemostatic pathways. The aim of this paper endorsed by the Liver Intensive Care Group of Europe was to provide an up-to-date overview of coagulation management in perioperative patients with chronic liver disease focusing on patient blood management, monitoring of hemostasis, and current role of hemostatic agents.

(*Cite this article as:* Biancofiore G, Blasi A, De Boer MT, Franchini M, Hartmann M, Lisman T, *et al.* Perioperative hemostatic management in the cirrhotic patient: a position paper on behalf of the Liver Intensive Care Group of Europe (LICAGE). Minerva Anestesiol 2019;85:782-98. DOI: 10.23736/S0375-9393.19.13468-2)

KEY WORDS: Liver cirrhosis; Hemostasis; Blood coagulation disorders; Perioperative care.

Approximately 29 million people in the European Union are diagnosed with chronic liver disease (CLD). Recent data from a large international prospective cohort study demonstrated that amongst patients undergoing elective surgery the prevalence of cirrhosis is 0.8% equating to approximately 25 million cirrhotic patients undergoing surgery each year worldwide.[1] Overall, the presence of cirrhosis is independently associated with 47% increased risk of postoperative complications and over two and a half increased risk of in-hospital mortality in patients undergoing elective surgery.[1] In particular, perioperative patients with CLD have long been assumed to have a ma-

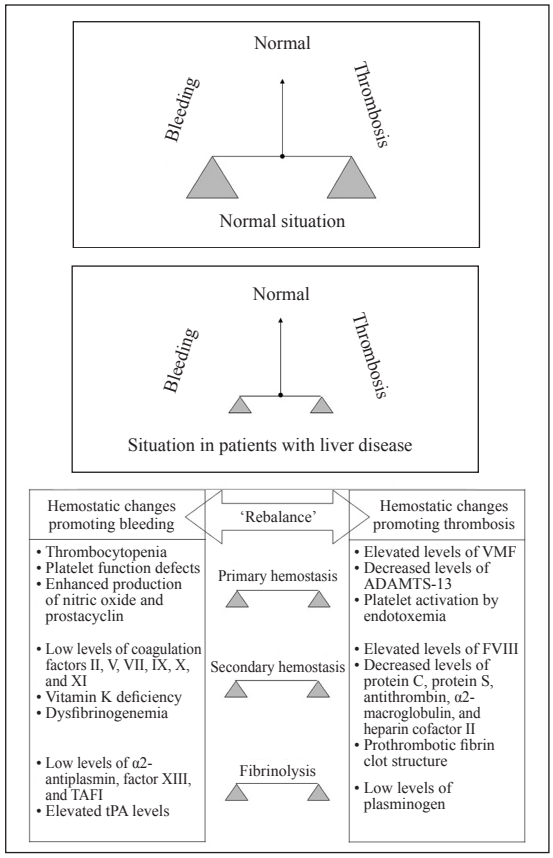

Figure 1.—The hemostatic balance.

jor bleeding risk on the basis of abnormal results for standard tests of hemostasis. However, recent evidence outlined significant changes to traditional knowledge and beliefs and, nowadays, it has been shown that patients with CLD may be in hemostatic balance as a result of concomitant changes in both pro- and antihemostatic pathways (Figure 1).

The aim of this position paper was to provide an up-to-date overview of coagulation management in perioperative patients with CLD focusing on patient blood management, monitoring of hemostasis, and current role of hemostatic agents.

In order to provide the clinical community with a straightforward and updated document, the Liver Intensive Care Group of Europe (LICAGE) nominated a panel of well-recognized international experts with the aim of addressing a debated topic (Supplementary Digital Material 1: Supplementary Text File 1).

Patient blood management in perioperative cirrhotic patients

Patient blood management (PBM) is a multidisciplinary, multimodal patient-centered strategy aimed at minimizing the utilization of blood products and improving patients' outcome.[2-5] One of the most important fields of application of PBM is the perioperative setting.[6, 7] Indeed, both anemia and transfusion have been associated with increased morbidity and mortality in surgical patients and the systematic application of a PBM program in the perioperative period has been consistently found to positively improve patients' clinical outcomes following surgery.[8] The concomitant presence, however, of medical illnesses may further complicate the implementation of PBM strategies in the surgical setting and in this context an excellent example is provided by advanced liver disorders. Anemia is a frequent finding in patients with cirrhosis, having a reported prevalence of approximately 60% of cases with a multifactorial etiology including deficiencies in iron/vitamin B12/folate, hypersplenism, malnutrition and complications related to the underlying cause such as alcohol-induced marrow aplasia or anemia related directly to viral liver disease or its treatment.[9] Thus, in the frame of a PBM program, potentially reversible causes of anemia should be diagnostically explored and corrected in such patients in the perioperative period, in order to reduce unnecessary transfusions. This consideration is particularly valid for patients undergoing liver transplantation, being blood transfusion considered a strong predictor of overall survival also after liver transplant (LT).[10] Another critical issue of a PBM program in surgical patients with liver cirrhosis is, however, the appropriate transfusion strategy.[11] A number of randomized trials and meta-analyses have consistently documented the superiority of restrictive (hemoglobin thresholds of less than 7 g/dL, less than 8 g/dL with coexisting cardiovascular disease) compared with liberal red blood cell (RBC) transfusion strategies (hemoglobin thresholds less than 9 g/dL to 10 g/dL) in surgical stable patients in terms of morbidity and mortality.[12, 13] However, in spite of such a transfusion approach endorsed by the majority of the nation-

al and international scientific societies and health authorities,[2, 14, 15] the real-life pertaining patients with liver cirrhosis is quite different. In a large, retrospective nationwide study conducted in the United Kingdom on transfusion practice for patients with cirrhosis, RBCs were transfused in over half of the cases with a presenting hemoglobin higher than 7 g/dL.[16] In addition, about one third of patients who were transfused with blood components for prophylaxis received fresh frozen plasma (FFP), whose clinical prophylactic effectiveness in patients with liver disorders was recently questioned by a large meta-analysis.[17] Viscoelastic test-guided management could help to reduce the use of FFP and guide the use of coagulation factor concentrates such prothrombin complex and fibrinogen concentrate, but more research is needed in this field.[18] The European Society of Anaesthesiology (ESA) guidelines recommend viscoelastic tests in the management of severe bleeding in LT (Grade 1C).[19] Finally, thrombocytopenia in cirrhosis, which has a multifactorial etiology (decreased thrombopoietin synthesis, sequestration in the spleen and increased turnover), may increase the surgical-related bleeding risk.[11] Although many experts recommend prophylactic platelet transfusion before surgery if platelet count is less than 50.000/mm^3, there is a substantial lack of evidence from literature to support this practice. Notably, it has been well established that LT can be performed in patients with platelet counts below 50.000/mm^3 without the requirement for any perioperative blood transfusions.[19]

LICAGE expert panel conclusions and recommendations are the following:

• preoperative anemia in cirrhotic patients should be identified and, whenever possible, corrected in order to minimize the risk of exposure to allogeneic RBCs transfusions (1B);

• FFP should be administered in the setting of coagulopathy-associated clinical significant bleeding, while prophylactic use of FFP is not recommended (2C);

• platelet concentrate should be administered in the setting of clinical significant bleeding. Target platelet levels of 50,000/mm^3 are recommended (2C).

Future directions and studies

Despite the complexity and the clinical relevance of the issue, there is a lack of studies on the perioperative care of patients with liver cirrhosis. Adequately powered randomized controlled trials are needed to optimize the PBM approach in surgical patients with advanced liver disease.

How to monitor hemostasis in patients with chronic liver diseases

Patients with advancing liver disease acquire abnormalities in all components that contribute to hemostasis,[20] with consequent alterations in laboratory tests of hemostasis. This section will describe clinically available and preclinical hemostatic tests with a description the caveats of each test, particularly for the patient with cirrhosis.

Platelet function tests

Thrombocytopenia is common in cirrhosis. However, *in-vitro* studies have suggested that thrombocytopenia is compensated for by highly elevated levels of the platelet adhesive protein von Willebrand factor (VWF).[21] There is ongoing debate on the functionality of platelets in patients with cirrhosis.[22] The ideal platelet function test would assess platelet adhesion, platelet activation, platelet aggregation, and platelet procoagulant activity. Unfortunately, all clinically available platelet function tests only assess one or two of these functions, and different platelet function tests may give very different information.[23, 24] For these reasons, platelet function testing in patients with cirrhosis may not be particularly useful.

The gold standard of platelet function, suspension aggregometry, frequently suggests platelet dysfunction in patients with cirrhosis. However, decreased aggregation may also be explained by thrombocytopenia. Many platelet function tests are in essence unsuitable for thrombocytopenic samples as the thrombocytopenia per se already affects the outcome of the test,[25] and alternatives such as flow-cytometric approaches may be more appropriate.[26] Most platelet function tests are insensitive for VWF levels, which makes them unsuitable to assess platelet function in cirrhotic pa-

tients who commonly have highly elevated VWF levels. The platelet function analyzer (PFA100) is the only clinically used platelet function test that tests platelet reactivity under conditions of flow, and therefore is sensitive for VWF levels. However, the PFA100 is also sensitive for thrombocytopenia and anemia, which obscures test results in cirrhosis.[27] Finally, thrombin generation tests in platelet rich plasma have been interpreted as a platelet function test.[28, 29] Although platelet procoagulant activity is an important contributor to hemostasis, the thrombin generation test is likely not ideal to assess procoagulant activity, for example because in the assay the platelets are only activated by thrombin which is known to elicit only a modest procoagulant response.[30]

Clinically, it is unclear whether a minimal platelet count in the patient with cirrhosis is required for optimal hemostasis. Some studies have suggested thrombocytopenia to increase bleeding risk,[31, 32] but it has not been established with this relation is causal, and whether platelet transfusion would decrease bleeding risk in such patients. Although it has been argued that a minimum of 50-60.000 platelets/mm3 are required, this number is extrapolated from thrombin generation studies,[29] which gives a misleading representation of platelet function.[30] Clearly, clinical studies are required to assess which platelet function tests correlate with clinical bleeding risk (spontaneous and procedure-related), and whether platelet transfusion decreases bleeding risk.

Coagulation tests

The prothrombin time (PT) and activated partial thromboplastin time (APTT) are frequently prolonged in patients with cirrhosis. However, these tests are only sensitive for plasma levels of procoagulants, as patients with cirrhosis have alterations in both pro- and anticoagulant proteins, they give an inaccurate representation of coagulation potential. The PT and APTT are therefore unrelated to bleeding risk, and should not be used to guide blood product transfusion in patients with cirrhosis.[33]

A test that much better represents coagulation balance is thrombomodulin-modified thrombin generation, which is sensitive for plasma levels of all pro- and anticoagulant proteins.[34, 35] However, this test is not widely available and in its current form unsuitable for clinical use. A whole blood thrombin generation point-of-care test is in development.[36] Thrombin generation in the absence of thrombomodulin gives misleading information as this test is insensitive for the anticoagulant protein C pathway, which is frequently affected in cirrhosis.[34, 37]

Fibrinogen levels are considered critical in the bleeding risk. As thrombin generation capacity appears preserved even in the sickest patients with cirrhosis,[38] prohemostatic therapy with fibrinogen concentrate may be more relevant than FFP transfusion both in prevention and in treatment of bleeding. However, clinical studies on efficacy of fibrinogen supplementation on prevention or treatment of bleeding are required to firmly establish the role of this intervention and plausible transfusion triggers.

Fibrinolytic tests

There is ongoing debate on whether hyperfibrinolysis is common in patients with advanced cirrhosis,[20, 39] which is at least in part driven by the lack of a validated global fibrinolytic test. It is therefore unknown what really defines a hyperfibrinolytic status in a patient with cirrhosis, although in some situations (*e.g.*, during liver transplantation) the combination of clinical bleeding and fibrinolysis testing (by viscoelastic testing, for example) convincingly demonstrates hyperfibrinolysis. Given the efficacy and safety of antifibrinolytic drugs in decreasing blood loss during liver transplantation,[40] it may be that antifibrinolytic drugs are underused in prevention or treatment of bleeding in other settings.

Whole blood hemostasis tests

Conceptually, rapid, point-of-care whole blood tests are ideally suited to monitor hemostasis in patients with cirrhosis. For this reason, clinicians are increasingly considering TEG or ROTEM as the gold standard, and ignore important limitations of these tests. Besides the lack of endothelial cells and appreciable flow rates, viscoelastic tests are insensitive for VWF and the protein C system, which are both considered important modulators of the hemostatic system in cirrhosis. Therefore, although thromboelastography points to a normal

hemostatic status in patients with cirrhosis, it likely still underestimates hemostatic potential. Nevertheless, viscoelastic tests may be useful to guide transfusion, particularly in the actively bleeding patient, but it is important to realize that cut-off values have not been definitively established.

LICAGE panel conclusions and recommendations are the following:

- PT and APTT are unrelated to bleeding risk. They should not be used to guide blood product transfusion in non-bleeding patients with CLD (1B);
- visco-elastic test reflects better bleeding risk than standard-laboratory tests, but have limitations (1C);
- flow cytometry appears to best capture the capacity of platelets to get activated, but clinical validation in patients with cirrhosis is required (1B).

Future directions and studies

Clinical cut-offs for VET should be determined in the future, particular for preproceural procedure. Thrombomodulin-modified thrombin generation seem to adequately depict the hemostatic rebalanced status in patients with CLD *in vitro* but clinical studies are needed to confirm this finding.

Current role of hemostatic agents

Evidence for the use of hemostatic drugs

The evidence for the safety, effectivity and indication of blood products like FFP, fibrinogen, prothrombin complex concentrates (PCCs), fibrinolysis inhibitors, desmopressin (DDAVP) and recombinant factor VII activated (rFVIIa) is rather limited particular in different settings.[41] Sufficient coagulation management should be done with coagulation factors, guided by viscoelastic tests (VET) (*e.g.* ROTEM or TEG). One major advantage in using VET is the tremendous shorter turnaround time.[42, 43]

Prophylaxis and therapeutic use of FFP

At the first attempts for liver transplantation, mass transfusion occurred very often. The common practice was a blind prophylactic transfusion of RBC, FFP and platelet concentrates on a 1:1:1. However, hence surgical expertise and hemostasis knowledge improved, this approach was left.[41]

Fresh frozen plasma contains all coagulation factors, anticoagulant and fibrinolytic proteins as well.[44] The activity of factors corresponds to physiological concentrations but decreases during freezing and thawing. To increase plasma activity of factors, large volumes (10 mL/kg to 30 mL/kg) are required.[45, 46] It is assumed that one unit of FFP increases coagulation factors by only 2-3%.[47] The required volume of FFP may trigger a transfusion associated circulatory overload.[48]

Another shortcoming of FFPs is the risk of pathogen transmission, because FFPs do not undergo pathogen inactivation at most hospitals. Moreover, thawing large volumes is time consuming, which could be harmful in term of a severe bleeding.

Fibrinogen concentrate

Fibrinogen decrease at first to critical levels in the case of bleeding[49] and during liver transplantation.[50] Fibrinogen serum levels, as the last factor in the coagulation cascade, determines together with platelets the clot firmness.[51] Fibrinogen concentrate (FC) as a lyophilized product can easily be reconstituted within few minutes at a high concentration (1 g/ 100 mL) and replacement can be done without a risk of hypervolemia. Disease transmission is abandoned due to pathogen inactivation. *In-vitro* addition of FC in plasma samples from cirrhotic patients improves clot firmness.[52]A recent review comparing FFPs and FC indicates a beneficial effects in trauma patients in favor of FC.[53]

Prothrombin complex concentrates

PCC can be stratified in four and three factors containing PCC. The infectious risk is very low due to virus elimination. PCCs are approved for vitamin K reversal, but perioperative application is common practice. Although data about PCC in LT is limited, a recent study indicated the efficacy in liver transplantation.[54]

The risk of thrombosis seems also reasonable.

Coagulation management in patients with ESLD was not associated with thrombosis.[55] A meta-analysis comparing FFPs and PCC for vitamin K reversal showed higher thrombotic risk for FFPs.[56] The proton trial, a prospective, randomized trial evaluated the prophylactic use of PCC on transfusion rate in liver transplantation.[57] However, no data are available yet.

Platelet concentrates

Platelet count is often decreased in end stage liver failure.[58] However, primary hemostasis may be preserved of even increased due to the increased serum levels of von Willebrand multimeres.[59] Notably, platelets are entrapped in the transplanted liver and are thought to be involved in sinusoidal obstruction syndrome, portopulmonary hypertension and hepatopulmonary syndrome.[60] Transfusion of platelets was associated with increased mortality rate in LT-patients,[61] therefore a restrictive use is recommended. Moreover, platelets, which are stored at room temperature are prone to bacterial contamination. Furthermore, platelets transfusion may cause febrile non-hemolytic transfusion reactions, allergic reactions, and transfusion associated lung injury.[62]

Recombinant activated factor VIIa

For the treatment of coagulopathies, recombinant activated factor VIIa (rFVIIa) is given in supra-physiological doses. It induces thrombin burst, platelet activation and clot formation.

While under physiologic conditions, tissue factor (TF) expressing cells are missing in the blood, during inflammatory diseases, like acute and chronic liver failure,[63, 64] TF is expressed by monocytes and endothelium, which may contribute to thrombosis in term of rFVIIa application.

Recombinant FVIIa is approved for the treatment of hemophilia with inhibitors, factor VII deficiency, and Glanzmann Thrombasthenia. Moreover, some studies suggest the use in blunt trauma and in neurosurgical patients.[65-67] However, a Cochrane review states that the evidence for this off label use is low and thrombotic risks might be higher than in hemophilia patients.[68] For liver transplantation, different systematic reviews, meta-analysis and Cochrane review demonstrated no beneficial effect of rFVIIa.[69-71]

Antifibrinolytics

Antifibrinolytics, like tranexamic acid (TXA) are used for both, prophylaxis and treatment of hyperfibrinolysis as well. Hyperfibrinolysis is common in liver transplantation and may be associated with bleeding.[72] In many cases hyperfibrinolysis occurs during anhepatic phase and after reperfusion. There are conflicting results about risks and benefits of antifibrinolytics. A recent Cochrane analysis of three trials with 1913 patients concluded no differences in term of mortality, rate of re-transplantation, and thromboembolic events.[70] However, the authors did not make a final recommendation in order that the studies were underpowered for assessment of thromboembolic events. There are numerous case reports on thromboembolic events with the use of antifibrinolytics which raise concern for prophylactic use.[73] Importantly, the incidence of intracardiac thrombosis (IC) (0.7-6.3%) and pulmonary embolism (0.4-4%) is high during liver transplantation procedures and mortality was found to reach up to 80%. The use of antifibrinolytics is guided by VETs at some transplantation centers, as hyperfibrinolysis can be detected by these devices.

Desmopressin

Desmopressin is an analog of vasopressin with reduced vasopressor activity. The agent stimulates the release of factor VIII:C and von Willebrand factor from the endothelium. Nasal desmopressin was found to reduce bleeding in dental extraction procedures in patients with liver cirrhosis.[74] In contrast desmopressin did not improve primary hemostasis in patients with liver cirrhosis.[75] However, it is important to note, that platelet activation is common due to the presence of highly active von Willebrand multimeres, which are not degraded as ADAMTS13 levels are lowered in these patients.

Potential indications for antithrombotic therapy

Recognizing, that thromboembolic events, portopulmonary hypertension, hepatopulmonary syndrome as well as the sinusoidal obstruction syndrome are potential risks of hypercoagulability in liver transplantation, it might be worth to

consider the potential beneficial effect of antithrombin.[60] It is well recognized that antithrombin is often reduced in liver transplantation, that decreased antithrombin levels favor thromboembolic events and heparin refractoriness. In pediatric liver transplantation, 70% of patients had reduced antithrombin activities.[76] In a pilot study Kaneko *et al.* hypothesized that substitution of antithrombin reduces both fibrinolysis and the decrease of platelets after transplantation.[77] It is important to state, that decreases in antithrombin are especially important in patients treated with coagulation factor-based coagulation management, while antithrombin is (partially) substituted with fresh frozen plasma. The fact, that there are no recommendations about indication, timing, dosing, and risks of antithrombin suggest an important avenue for future research. Conventional antithrombotic treatment is discussed below.

LICAGE panel conclusion and recommendations are the following:

- prophylactic FFP transfusion should be avoided (1C);
- in bleeding patients, once fibrinogen and platelets are replaced and fibrinolysis is excluded, the administration of PCCs may be considered (1C);
- there is no indication for rFVIIa (1A);
- good evidence of beneficial effect of antifibrinolytics (2C).

Future directions and studies

More evidence, hopefully from RCTs, is needed addressing the efficacy and safety of using coagulation factors (namely PCCs) in LT

Multidisciplinary approach to avoid periprocedural bleeding of the cirrhotic patient

Periprocedural bleeding in cirrhotic patients is influenced by multiple factors, like preoperative condition of the patient, anesthesiological care and surgical techniques. A multidisciplinary approach with close collaboration between all concerned disciplines is therefore fundamental.

Preoperative condition

Avoiding periprocedural bleeding already starts preoperatively. Risk factors for periprocedural bleeding should be minimized whenever possible; marginal nutritional state should be avoided, portal hypertension treated, and renal function optimized prior to surgery.[78]

As supported by the NICE guidelines, most centers routinely perform preoperative hemostasis tests.[79] In cirrhotic patients though, prophylactic transfusion based on preoperative hemostasis tests should be avoided.[33, 80] The efficacy of prophylactic transfusion in cirrhotic patients has never been proven and in fact may be counterproductive. Despite improvement of platelet count or PT after transfusions, the volume of transfusions cause increase in portal and central venous pressure and subsequent periprocedural bleeding risk. Besides that, blood transfusion during liver transplantation is associated with increased mortality, brings considerable costs and a risk of devastating transfusion reactions. Therefore, a wait-and-see policy is preferred, in which preoperative prolonged coagulation tests should be accepted, and blood components only be transfused when active, nonsurgical bleeding occurs.[81] This policy is supported by the increasing evidence of a 'rebalanced' hemostatic profile in cirrhotic patients, with adequate thrombin generation capacity despite prolonged conventional coagulation test.[33, 80]

Anesthesiological care

Anesthesiological strategy to minimize periprocedural blood loss should focus on restrictive fluid infusion policy, to maintain a low central venous pressure (CVP). The CVP, which is already elevated in cirrhotic patients, is directly related to the hepatic vein pressure and is almost linear correlated with the amount of blood loss.[82] Maintenance of a low CVP (<5 cmH_2O) and preoperative CVP reduction by phlebotomy, appeared a beneficial strategy to reduce blood loss during hepatectomy or liver transplantation.[82-84] Although these studies present some interesting results, there are concerns which should be considered. The study was performed 20 years ago and, since then, many surgical and anesthetic improvements occurred making it difficult to

extrapolate this study's results to present.[82] In a more recent study Massicotte *et al.*[83] demonstrated that cirrhotic patients benefit from restrictive fluid management and that the benefit was due to a reduced portal vein pressure, resulting from phlebotomy, rather than from a reduced CVP. Another important anesthetic focus for surgery in cirrhotic patients is monitoring of coagulation abnormalities and its correction, mainly by administration of blood components like fresh frozen plasma (FFP), fibrinogen or platelet concentrates. As mentioned above, also hemostatic drugs can be administered. Routine correction of abnormal coagulation tests with FFPs is not effective in reducing periprocedural blood loss.[54, 83, 85]

At present, in a variety of surgical settings cell salvage has been adopted in order to reduce allogenic blood transfusion rates. Its efficacy in reducing blood transfusion in liver transplantation patients was demonstrated.[86, 87] Besides that, in liver transplantation the cell saver could also be used to transfuse the previous obtained blood during phlebotomy.[88] Lastly, hypothermia and metabolic acidosis should be avoided because they may aggravate coagulation abnormalities.[78]

Surgical techniques

To reduce blood loss during liver transplantation, several surgical techniques were modified over time. In the 1980s the veno-venous bypass was introduced. Due to the decompression of splanchnic and retroperitoneal circulation, less hemodynamic changes occurred during anhepatic phase, leading to a reduction of blood loss.[89]

A second important step was cava sparing liver transplantation, the so-called piggyback technique, in which the recipients inferior vena cava (IVC) is retained and the donor IVC is anastomosed to it. This enables partial clamping and avoids interruption of blood flow through the IVC, subsequently the venous return to the heart can be maintained. This facilitated better intraoperative hemodynamic stability with a low CVP. Secondly, the piggyback technique eliminated the need for dissection of the retroperitoneum in a patient with portal hypertension and multiple venous collaterals.[78] This technique resulted in liver transplantation with less blood transfusion and shorter warm ischemia times.[90, 91] A next step, to decrease portal venous stasis during hepatectomy, the piggyback technique was combined with temporary portocaval shunts by using end to side portocaval anastomosis or extracorporeal catheters. By reduction of the portal venous pressure, hemodynamic stability improved and blood loss was reduced. This simple and effective combined technique reduced the amount of blood transfusions and hepatic injury, without prolonging operation time. Nonetheless, this method must be further explored in a prospective RCT.[92]

LICAGE panel conclusion and recommendations are the following:

- periprocedural bleeding in cirrhotic patients is influenced by multiple factors including preoperative condition of the patient, anesthesiological care and surgical techniques, which makes a multidisciplinary approach fundamental (1B).
- in cirrhotic patients with preoperative prolonged coagulation tests, a wait-and-see policy is preferred over prophylactic transfusions; blood components should only be transfused when active non-surgical bleeding occurs (1C).
- periprocedural maintenance of a low CVP is a beneficial strategy to reduce blood loss during surgery in cirrhotic patients and can be realized by restrictive fluid infusion policy (2B).
- the piggyback technique (2A) and the adoption of intraoperative portocaval shunts (2B) are effective surgical techniques to reduce periprocedural bleeding in liver transplantation.

Future directions and studies

The transplant community should work on better volume assessment tools and better preoperative assessment of bleeding risk factors.

Perioperative thrombotic risk

Thrombotic complications in patients with cirrhosis occur with a greater frequency than in the general population. Risk factors for thrombosis include inherited and acquired deficiency of factors involved in anticoagulation mechanisms, venous stasis and possibly local factors related to the endothelium. The following section briefly discuss the management of perioperative thrombotic events in patients with cirrhosis, being PVT the most frequent.

Portal vein thrombosis

Portal vein thrombosis (PVT) represents the most common thrombotic complication occurring in cirrhosis, with 1-year incidence ranging from 7.4% to 11%[93-101] up to 24% in cirrhotic patients with HCC.[100] Pathogenesis of PVT is likely to be multifactorial and both local and systemic factors can be involved.[102] The risk of PVT has been shown to be independently associated with the severity of liver disease and severity of portal hypertension.[103] PVT in cirrhotic patients is often asymptomatic or diagnosed in coincidence with variceal bleeding or abdominal pain.[104] After the development of PVT, progression of thrombosis has been reported in 50% of cases in average at two-year follow-up.[105, 106]

Portal thrombosis by itself increases the risk of variceal bleeding and related mortality.[107] Correct staging with CT scan and classification according to Yerdel is recommended.[103] In the LT setting, when PVT is complete (or grade III according to Yerdel's classification), post-transplant survival rates are compromised with an HR of 5.65 (95% CI: 2-15.96), P=0.001 and HR 2.48 (95% CI: 0.99-6.17) for 30 day and one year post-LT mortality, respectively.[108] Non-anatomic solutions, particularly porto-caval hemi-transposition (PCHT), do not solve portal hypertension[109-111] and 1-year mortality has been reported to be 40%. The aim of anticoagulation therapy should be the repermeation of the vessel or reduction of thrombosis extension in order to ensure anatomical reconstruction. To date, data on the efficacy and safety of medical anticoagulation to treat PVT come from seven cohort studies which included 258 patients, most with partial PVT.[99, 106, 111-115] Globally, the re-permeation rate ranged from 56% to 76%. When anticoagulation is withdrawn, recurrence of thrombosis is frequent.[111] The anticoagulant treatment was not associated with a significant risk of bleeding. Overall, possibly related bleeding complications were seen in only 19/230 (8.2%) patients and not correlated with portal hypertension. In cirrhotic patients, TIPS can be considered to treat PVT in case of thrombus progression despite adequate anticoagulant treatment, in case there is an absolute contraindication to anticoagulation or in case of no response after a maximum of six months of anticoagulation treatment. Recanalization of the PV is feasible in about 50% to 80% of patients.[105] In presence of extensive thrombosis recanalization of the portal vein by percutaneous approach with TIPS placement is feasible in expert centers with acceptable complication rate.

LICAGE panel conclusion and recommendations are the following:

- in patients with cirrhosis a Doppler ultrasound at 6-month intervals should be used as a screening for the detection of PVT (C1);
- CT scan/MRI are recommended to evaluate extension of PVT, adopting the Yerdel's classification (B1);
- anticoagulation is recommended for a period of at least six months (B1);
- in extensive thrombosis or in those patients not responding to anticoagulation transjugular intrahepatic portosystemic shunt could be considered (B2).

Deep vein thrombosis and pulmonary embolism

The association between cirrhosis and risk of pulmonary thromboembolism (PE) or deep vein thrombosis (DVT) amongst hospitalized patients with cirrhosis has been evaluated in retrospective case control studies in which 0.8-7% of cirrhotic patients presented with thrombosis in these sites Cirrhosis carries a 1.7-fold increased relative risk of venous thrombosis compared to the general population.[116-118] Interestingly, traditional markers of coagulation impairment in liver disease were not correlated with VTE, but low serum albumin is independently predictive in two studies.[116, 117] Current guidelines do not recognize the thromboembolic risk associated with chronic liver disease. The Padua Prediction Score may be used to decide if patients should be treated with primary prophylaxis or not, although further clinical validation of this score in patients with cirrhosis is required.[119] The reported use of prophylactic anticoagulation for VTE in patients with chronic liver disease (21-25%) remains significantly lower than in other in-patients.[120] The interim suggestion is that VTE pro-

phylaxis is considered on a case-by-case basis in hospitalized cirrhotic patients, based on risk factor assessment for VTE (length of hospitalization, prolonged immobilization, cancer, previous VTE and recent trauma/surgery). If anticoagulation is contraindicated, then mechanical prophylaxis should be considered.[121] The anti-Xa assay cannot be used to monitor LMWH activity in cirrhotic patients. While VKA are desirable for their low cost and oral administration, dosing of VKA in cirrhosis patients is particularly challenging due to pre-existing elevation of the INR. Moreover, an increased risk of bleeding has been reported in patients with PLT count less than 50.000 UI/mL.[114]

LICAGE panel conclusion and recommendations are the following:

• patients with cirrhosis are not protected against VTE and should receive antithrombotic prophylaxis in conditions with increased risk for VTE according to standard criteria (C2);

• when low molecular weight heparins (LMWH) are used laboratory monitoring should not be used (C2).

Perioperative thrombotic complications in liver transplantation: intraoperative IC and pulmonary emboli

The incidence of pulmonary emboli (PE) ranges from 1.2% to 6.25% and IC between 0.71% up to 6.25%, occurring mostly during the preanhepatic phase or immediately after reperfusion.[122-124] Large amounts of blood products, intravascular catheters, prolonged surgery and clamping, have been identified as risk factors.[73, 124] No significant increase has been observed with the use of fibrinogen[125] nor antifibrinolytics,[126] but rFVIIa has been associated with an increased incidence of thrombotic events.[127] PE and IC both should be suspected in case of increased pulmonary artery pressure or hemodynamic instability not responding to supportive therapy. Intraoperative transesophageal echocardiography (TEE) allows the confirmation. Despite therapy with tissue plasminogen activator has been shown to be superior to embolectomy or heparin, mortality remains very high (45-68%).[73, 124]

DVT

After liver transplantation, incidence ranges from 3.5% to 8.6%.[124, 128] Thromboprophylaxis is indicated. In specific conditions: thrombophilia, prolonged immobilization and large blood product transfusion, therapeutic doses of anticoagulation may be indicated.[124, 129, 130] Treatment is recommended with LMWH[131] followed by oral anticoagulants. Unfractioned heparin (UFH) cannot be monitored.[132] Vena cava filter insertion is indicated when anticoagulation is not possible.[133]

Hepatic artery thrombosis

The incidence ranges from 2.5% to 6%.[134] Early hepatic artery thrombosis (HAT) leads to acute graft dysfunction; late HAT leads to ischemic cholangiopathy.[135] Anatomic/mechanical factors are mostly involved, but etiology of cirrhosis (familial amyloidotic polyneuropathy, autoimmune, cholestasis and hepatocarcinoma), thrombophilia donor/recipient, high perioperative transfusion;[128, 136, 137] PVT[138] and reduced postanastomotic hepatic artery flow were associated with increased risk of HAT.[139] Early HAT needs immediate graft repermeabilization by endovascular mechanical/pharmacologic thrombolysis, or surgical reconstruction.[140] Failure of the previous approaches requires urgent re-transplantation.[141]

Thromboprophylaxis is recommended in small or "non-anatomical" anastomosis, living donor LT, split, poor arterial flow and pretransplant PVT.[80, 139] Aspirin was associated with significantly lower incidence of early and late HAT.[142-144] UFH or LMWH plus aspirin have been proposed in individuals at higher risk.[145]

PVT after LT

PVT after LT is relatively rare at 0.5-2%. However, early rethrombosis in recipients with PVT prior to LT ranged from 5% to 21%.[103, 146] Intraoperative thrombectomy and sever portal hypertension have been identified as risk factors.[147, 148] Early PVT can necessitate urgent retransplantation. Reoperation is the most successful option but percutaneous mechanical/pharmacologic thrombolysis, transjugular approach and systemic heparinization have been attempted.[124, 130, 149]

Prophylactic anticoagulation is recommended in those patients with previous complete PVT or undergoing "non-anatomical" anastomosis for at least three months.[150]

LICAGE panel conclusion and recommendations are the following:

• when intra-cardiac or pulmonary thrombi are suspected during LT, confirmation by intraoperative TEE is recommended (C1);

• systematic early abdominal US is recommended to confirm vascular graft patency (B2);

• anticoagulation in LT is recommended in complicated vascular anastomosis, overtransfusion, pretransplant PVT (especially when intraoperative thrombectomy), and additional thrombophilic conditions (B2);

• aspirin is recommended to prevent both early and late HAT in case of small vessels (living donor LT, split), complicated anastomosis, poor hepatic arterial flow and pretransplant PVT (B1).

Future directions

Future studies should prove efficacy and safety of the different antithrombotic agents in cirrhotic patients, which includes to work out an appropriate monitoring for these drugs.

Antithrombotic treatment management in patients with cirrhosis

The current literature show that anticoagulant therapy in cirrhotic patients is safe as bleeding events do not occur at higher rates than in untreated patients. Anticoagulant therapies include unfractioned heparin, low molecular weight heparins and fondaparinux for acute treatment, and low molecular weight heparins and vitamin K antagonists for long-term treatment. No robust data currently support the use of direct oral anticoagulants (DOACs) in patients with cirrhosis and PVT and the safety and efficacy of DOACs in this setting is still unclear. However, some patients with cirrhosis can receive DOACs for other indications. Patients with cirrhosis can also receive antiplatelet agents because of coronary artery disease. There are no specific recommendations for patients with liver disease on antithrombotic treatment. General recommendations may be used as a guide taking into account the abnormal glomerular filtrate and the thrombocytopenia frequently see in this population (Table I).

TABLE I.—*Recommended antithrombotic treatments in patients with glomerular filtrate >50 mL/mL.*

Antithrombotic treatments	Days/hours of suspension
Direct oral anticoagulants	
Rivaroxaban	1
Edoxaban	1
Apixaban	2
Dabigatran	2
Antiplatelet agents	
Cyclooxygenase inhibitors	
Acetylsalicylic acid (ASA) 100 mg	3
ASA, 300 mg	5
Trifusal	5
P2y12 inhibitors	
Ticlopidina	7
Clopidogrel	5
Prasugel	7
Ticlagrelor	7
Cangrelor	1h
IIbIIIa inhibitors	
Abcibximab	12h
Tirofiban	8h
Eptifibatide	8h

There are no specific LICAGE recommendations for patients with liver disease on anticoagulation/antiplatelet agents management. General recommendations may be considered when surgery or other invasive procedures are required in patients under antithrombotic treatment (C2).

Key messages

• Preoperative anemia in cirrhotic patients should be identified and, whenever possible, corrected in order to minimize the risk of exposure to allogeneic RBCs transfusions. FFP should be administered in the setting of coagulopathy-associated clinical significant bleeding, while prophylactic use of FFP is not recommended. Platelet concentrate should be administered in the setting of clinical significant bleeding. Target platelet levels of 50,000/mm^3 are recommended.

• PT and APTT are unrelated to bleeding risk. They should not be used to guide blood product transfusion in non-bleeding patients with CLD. Visco-elastic test reflects better bleeding risk than standard-laboratory tests, but have limitations.

• Prophylactic FFP transfusion should be avoided. In bleeding patients, once fibrinogen and platelets are replaced and fibrinolysis is excluded, the administration of PCCs may be considered. There is no indication for rFVIIa with good evidence of beneficial effect of antifibrinolytics.

• Periprocedural bleeding in cirrhotic patients is influenced by multiple factors such as the preoperative condition of the patient, anesthesiological care and surgical techniques, which makes a multidisciplinary approach fundamental. In cirrhotic patients with preoperative prolonged coagulation tests, a wait-and-see policy is preferred over prophylactic transfusions; blood components should only be transfused when active non-surgical bleeding occurs. Periprocedural maintenance of a low CVP is a beneficial strategy to reduce blood loss during surgery in cirrhotic patients and can be realized by restrictive fluid infusion policy.

• In patients with cirrhosis a Doppler ultrasound at 6-month intervals should be used as a screening for the detection of PVT. CT scan/MRI are recommended to evaluate extension of PVT, adopting the Yerdel's classification. Anticoagulation is recommended for a period of at six least months. In extensive thrombosis or in those patients not responding to anticoagulation transjugular intrahepatic portosystemic shunt could be considered.

• Patients with cirrhosis are not protected against VTE and should receive antithrombotic prophylaxis in conditions with increased risk for VTE according to standard criteria. When low molecular weight heparins (LMWH) are used laboratory monitoring should not be used.

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Conflicts of interest.— Matthias Hartmann received unrestricted grant from CSL-Behring for retrospective data acquisition of liver transplantation procedures.

Comment in: Sollazzi L, Perilli V. Endstage liver disease: a delicate balance of bleeding and thrombosis. Minerva Anestesiol 2019;85:712-4. DOI: 10.23736/S0375-9393.19.13859-X.

Article first published online: April 2, 2019. - Manuscript accepted: April 2, 2019. - Manuscript revised: March 1, 2019. - Manuscript received: November 19, 2018.

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