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Transfusion strategies in patients with cirrhosis

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Abstract

Bleeding related to portal hypertension and coagulopathy is a common complication in patients with cirrhosis. Complications and management of bleeding is a significant source of healthcare cost and utilization, as well as morbidity and mortality. Due to the scarcity of evidence surrounding transfusion strategies and hemostatic interventions in patients with cirrhosis, there has been significant debate regarding the best practice. Emerging data suggest that evidence supporting transfusion of packed red blood cells to a hemoglobin threshold of 7-8 g/dL is strong. thrombopoietin (TPO) receptor agonists have shown promise in increasing platelet levels and reducing transfusions preprocedurally, although have not specifically been found to reduce bleeding risk. Data for viscoelastic testing (VET)-guided transfusions appear favorable for reducing blood transfusion requirements prior to minor procedures and during orthotopic liver transplantation. Hemostatic agents such as recombinant factor VIIa, prothrombin complex concentrates, and tranexamic acid have been examined but their role in cirrhotic patients is unclear. Other areas of growing interest include balanced ratio and whole blood transfusion. In the following manuscript, we summarize the most up to date evidence for threshold-guided, VET-guided, balanced-ratio, and whole blood transfusions as well as the use of hemostatic agents in cirrhotic patients to provide practice guidance to clinicians.

KEYWORDS

blood coagulation disorders, blood component transfusion, gastrointestinal hemorrhage, liver cirrhosis, viscoelastic testing

1 | INTRODUCTION

Upper gastrointestinal bleeding (UGIB) results in nearly 300 000 hospitalizations and 15 000-30 000 deaths per year in the United States.[1] Upper gastrointestinal bleeding related to portal hypertension is a serious complication in patients with cirrhosis. Variceal UGIB represents 60%-65% of UGIB presentations in patients with cirrhosis and is associated with a mortality rate of up to 30% during their initial hospitalization.[2,3] Bleeding in general is a significant source of healthcare cost and utilization, as well as morbidity and mortality in patients with chronic liver disease.

All clotting factors except for Von Willebrand factor and endothelial derived Factor VIII are produced by the liver; therefore, cirrhosis can lead to multiple coagulation abnormalities detectable on a variety of commonly used assays. thrombopoietin, the main regulator of platelet production, is also hepatically synthesized. This coupled with splenomegaly from portal hypertension often results in the characteristic thrombocytopenia of liver disease.[4] In the last several decades, there has been increasing awareness that the decreased level of procoagulants in cirrhosis is also accompanied by reductions in levels of anticoagulants; a concept termed "rebalanced hemostasis".[5,6] These physiologic conditions complicate our ability to interpret basic laboratory coagulation tests in patients with cirrhosis and convolute appropriate management of cirrhosis-related acute hemorrhagic events.

Due to the lack of evidence surrounding transfusion strategies in patients with cirrhosis, there has been significant debate regarding

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the best practice. Current standard of care includes threshold-based transfusions: American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend conservative transfusion parameters (threshold hemoglobin of 7 g/dL).[2] There is a paucity of data regarding the appropriate use of transfusions to address coagulopathy found in liver disease, as well as threshold-based management of thrombocytopenia.[7] Currently, a number of transfusion strategies are employed including threshold-based, viscoelastic testing (VET)-guided, balanced-ratio, and whole blood transfusions. A number of hemostatic agents have also been studied in patients with cirrhosis. Given the lack of clear evidence and guidelines, we review what is currently known and highlight areas for potential future research.

2 | THRESHOLD-BASED TRANSFUSION STRATEGIES

Threshold-based transfusions for hemoglobin in the setting of an acute bleed are the current standard of care as recommended by as AASLD.[2] A recent randomized controlled trial (RCT) of patients presenting with GI bleed showed that a "restrictive" packed red blood cell (pRBC) transfusion strategy (hemoglobin threshold of 7 g/dL) was associated with a significant decrease in mortality compared to a "liberal" transfusion strategy (hemoglobin threshold of 9 g/dL). A subgroup analysis of this RCT showed that there was also significantly lower early rebleeding and mortality rates in patients with cirrhosis, particularly those with Child-Turcotte-Pugh class A and B.[8] Thus, current guidelines recommend blood transfusions to a goal of 7-8 g/dL in patients with cirrhosis[9,10]; however, there are still no guidelines addressing the use of other plasma-based blood products. A compilation of the current guidelines can be found in Table 1. Furthermore, transfusion of blood products may increase portal pressures or alter coagulation parameters in patients with cirrhosis, thus increasing the risk of further bleeding or predispose to rebleeding[11,12] Lastly, while some provide preoperative pRBC transfusion to certain thresholds, this practice is not well studied or universally practiced.

3 | THROMBOCYTOPENIA AND THROMBOPOIETIN RECEPTOR AGONISTS

Thrombocytopenia is a common complication in liver disease. The development of thrombocytopenia in cirrhosis is multifactorial and includes splenic sequestration and decreased production of hematopoietic growth factor thrombopoietin (TPO) in the liver.[13] There is currently no consensus on the appropriate threshold value for platelet transfusion in cirrhotic patients but clinicians typically transfuse to a threshold of 50×10^9/L in the event of a bleed or an upcoming invasive procedure.[14,15] Another factor that complicates recommendations on platelet transfusion is that platelet quantity does not reflect platelet function. Platelet function, especially in a patient with cirrhosis, can be negatively affected by a myriad of factors such as medications, infection, and renal clearance. One study observed that in vitro platelet-related thrombin production (as an indirect measure of platelet function) was adequate in patients with cirrhosis having platelet levels of at least 56×10^9/L.[16] However, there have been no clinical trials showing that the threshold of 50×10^9/L is an appropriate target to prevent bleeding. In regards to paracentesis, one prospective study of 1100 large-volume paracentesis documented no bleeding complications with preprocedure or postprocedure transfusions required despite platelet counts as low as 19×10^9/L.[17] As such, the AASLD does not recommend the routine prophylactic use of fresh frozen plasma or platelets before paracentesis.[18] Lastly, the decision to transfuse platelets must always be weighed against the risk of platelet-antibody production, transfusion reactions, and the possibility of increasing portal venous pressures.

thrombopoietin, the main stimuli for thrombopoiesis, is synthesized by the liver and degraded by circulating platelets. Binding of TPO to the TPO receptor induces a cascade of cellular reactions that leads to megakaryocytic proliferation and differentiation and thereby the production of platelets.[19] Patients with cirrhosis have been found to have lower serum TPO levels than healthy controls.[20] TPO receptor agonists have shown promise in increasing platelet levels in patients with cirrhosis and preventing platelet transfusions to achieve a threshold of 50×10^9/L. Avatrombopag and Lusutrombopag are currently the only two FDA-approved orally administered TPO receptor agonists.

In ADAPT-1 and ADAPT-2, the Avatrombopag groups compared to the placebo groups had a significant reduction in the studies' primary endpoint of platelet transfusions or rescue procedures for bleeding.[21] Lusutrombopag was studied in thrombocytopenic patients with child-Pugh Class A or Class B cirrhosis expecting to undergo a non-emergency invasive procedure. Significantly more patients in the Lusutrombopag group did not require platelet transfusion prior to their procedure or rescue therapy for bleeding after the procedure compared to placebo.[22] Based on these studies, TPO receptor agonists have demonstrated reduced platelet transfusion but not reduced bleeding. Lastly, the use TPO receptor agonists is limited by a slow onset of action (delay of 5 days or more before platelet levels rise with a peak of 12-14 days) and therefore may require advanced planning.[23]

4 | PT/INR AND FRESH FROZEN PLASMA

The protime assay (PT) was developed in 1935 as a means to investigate the coagulopathy associated with obstructive jaundice.[24] The international normalized ratio (INR) was introduced in 1984 as a means of standardizing results to improve safety of oral anticoagulants. Over the years, the PT/INR became the test of choice to investigate congenital or acquired coagulopathies and as a way to monitor treatment with vitamin K antagonists. More literature is now available suggesting that the INR in patients with cirrhosis may not be predictive of bleeding complications.[25] Protime assay is

TABLE 1 Summary of current guidelines from major societies

Society	Practice guideline	Recommendation
American Gastroenterology Association (AGA) 2019	Clinical practice update: coagulation in cirrhosis[15]	Global tests of clot formation, such as rotational thromboelastometry, thromboelastography, sonorheometry, and thrombin generation, may eventually have a role in the evaluation of clotting in patients with cirrhosis, but currently lack validated target levels. In general, clinicians should not routinely correct thrombocytopenia and coagulopathy before low-risk therapeutic paracentesis, thoracentesis, and routine upper endoscopy for variceal ligation in patients with hepatic synthetic dysfunction–induced coagulation abnormalities. Blood products should be used sparingly because they increase portal pressure and carry a risk of transfusion-associated circulatory overload, transfusion-related acute lung injury, infection transmission, alloimmunization, and/or transfusion reactions. The following transfusion thresholds for management of active bleeding or high-risk procedures may optimize clot formation in advanced liver disease: hematocrit ≥25%, platelet count >50 000, and fibrinogen >120 mg/dL. Commonly utilized thresholds for international normalized ratio correction are not supported by evidence. Thrombopoietin agonists are a good alternative to platelet transfusion, but require time (about 10 d) to elevate platelet levels. The large volume of fresh frozen plasma required to reach an arbitrary international normalized ratio target, limitations of the usual target, minimal effect on thrombin generation, and adverse effects on portal pressure limit the utility of this agent significantly. The 4-factor prothrombin complex concentrate contains both pro- and anticoagulant factors that offer an attractive low-volume therapeutic to rebalance a disturbed hemostatic system. However, dosage is, in part, based on international normalized ratio, which is problematic in cirrhosis, and published experience in liver disease is limited. Antifibrinolytic therapy may be considered in patients with persistent bleeding from mucosal oozing or puncture wound bleeding consistent with impaired clot integrity. Both ε-aminocaproic acid and tranexamic acid inhibit clot dissolution. Neither is believed to generate a hypercoagulable state, although both may exacerbate pre-existing thrombi.
American Gastroenterology Association (AGA) 2019	Clinical practice update on surgical risk assessment and perioperative management in cirrhosis[30]	*The INR is not predictive of bleeding complications in patients with cirrhosis, and "prophylactic" preoperative fresh frozen plasma transfusions are not recommended* … in vitro *and retrospective cross-sectional studies have shown that platelet counts above 50 000/μL are adequate to allow clot formation in most patients with cirrhosis. Prophylactic transfusions to raise the platelet count to higher levels are unlikely to be beneficial and may expose the patient to complications of transfusions, volume overload, or unexpected thrombosis.* *Low fibrinogen levels are associated with an increased bleeding risk, and levels <100 mg/dL are associated with a risk of inhibiting clot formation in patients with cirrhosis… Although no controlled trials of the efficacy of fibrinogen transfusion in patients with cirrhosis have been undertaken, it seems physiologically reasonable to replete fibrinogen levels with infusions of cryoprecipitate before high-risk surgical procedures to allow the substrate for adequate clot formation.* If available, viscoelastic testing should be considered before and during surgical procedures in patients with cirrhosis to help guide a rational transfusion strategy.
European Association for the Study of the Liver (EASL) 2018	Clinical practice guidelines for the management of patients with decompensated cirrhosis[10]	A restrictive transfusion strategy is recommended in most patients with a hemoglobin threshold for transfusion of 7 g/dL and a target range of 7-9 g/dL; **Evidence Level I; Grade 1** *[in regards to LVP] there are no data supporting the prophylactic use of fresh frozen plasma of pooled platelets, even though these are employed in many centers when prothrombin activity is below 40% and platelet count < 40 000/ll. LVP should be avoided in the presence of disseminated intravascular coagulation.*
American Association for the Study of Liver Diseases (AASLD) 2016	Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance[29]	PRBC transfusion should be done conservatively, starting to transfuse when the hemoglobin reaches a threshold of around 7 g/dL with the goal of maintaining it between 7 and 9 g/dL. *Regarding correction of coagulopathy, RCTs of recombinant factor VIIa have not shown a clear benefit, and therefore correcting the international normalized ratio (INR) by the use of fresh frozen plasma or factor VIIa is not recommended, particularly given that INR is not a reliable indicator of coagulation status in cirrhosis.* *No recommendations can be given regarding platelet transfusion in patients with variceal hemorrhage*

(Continues)

TABLE 1 (Continued)

Society	Practice guideline	Recommendation
Baveno VI faculty 2015	Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension[9]	Packed red blood cells transfusion should be done conservatively at a target hemoglobin level between 7 and 8 g/dL, although transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status, and ongoing bleeding. **Evidence Level 1b; Grade A** Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data. **Evidence Level 5; Grade D** PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis. **Evidence Level 1b; Grade A**
The European Haematology Association (EHA) and others 2006	Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding[45]	Based on the currently available evidence, rFVIIa should not be used in patients with Child-Pugh A cirrhosis. **Evidence Grade B** In patients with Child-Pugh B and C cirrhosis, the efficacy of rFVIIa in patients with bleeding episodes (esophageal and UGI bleeding, and bleeding after percutaneous needle biopsy) is uncertain. **Evidence Grade C**

responsive to deficiencies of many pro-coagulation factors (VII, X, C, II, and fibrinogen). In liver disease, this test becomes difficult to interpret because not only are pro-coagulant factors decreased but anticoagulant factors such as antithrombin, protein C and protein S are as well. The consensus guidelines in both the anesthesiology and interventional radiology literature, although not specific to patients with liver disease, still recommend threshold-based transfusion to an INR goal prior to procedures. Society of Interventional Radiology guidelines recommend transfusions to achieve a goal INR <1.5 for moderate to significant bleeding risk procedures and INR <2.0.[26] Many providers choose not to use threshold-based INRs for cases of patients with cirrhosis. Lastly, there is no evidence to support prophylactic correction of elevated INR prior to large-volume paracentesis.[17]

Fresh frozen plasma (FFP) has traditionally been used to correct coagulopathy in patients with elevated INR. In vitro studies have evaluated the efficacy of correcting coagulopathy in cirrhosis. One study evaluated in vitro thrombin generation in plasmas from patients with cirrhosis when mixed with appropriate amounts of pooled normal plasma (PNP). The authors found that plasma shortens the prolonged thrombin time; however, thrombin formation remained unchanged even after mixing with PNP. This study calls into question the significance of the PT and APTT shortening caused by FFP if the in vitro generation of thrombin formation is not significantly changed.[27] Another recent study examined endogenous thrombin potential with thrombomodulin after FFP transfusion in cirrhotic patients.[28] They found that although FFP transfusion ameliorated conventional coagulation tests and enhanced thrombin generation in a very limited number of patients, 34% of cases had decreased thrombin generation in response to FFP transfusion. The group speculated that FFP transfusion could decrease thrombin generation by replenishing protein C, giving another reason against FFP transfusions based on arbitrary PT and APTT cutoffs. Currently, The AASLD and American Gastroenterology Association (AGA) do not recommend use of FFP as part of the management of portal hypertensive bleed or for prophylactic use preoperatively or prior to paracentesis; the rationale being that INR is not a reliable indicator of coagulation status in cirrhosis.[29,30] Lastly, transfusion with FFP also comes with the risk of increasing portal hypertension and hypervolemia.[31]

5 | FIBRINOGEN

Fibrinogen is a glycoprotein that is synthesized in hepatocytes. Once fibrinogen is cleaved to fibrin, it binds platelets and promotes clot formation. Fibrinogen levels are normal or slightly increased in patients with mild or moderate cirrhosis; however, patients with severe cirrhosis, particularly those in decompensated cirrhosis, often have decreased levels.[32] Liver dysfunction causes alterations in fibrinogen function by synthesis of abnormal fibrinogen, termed dysfibrinogenemia,[33] decreased production of fibrinogen and hyperfibrinolysis, as described below. Dysfibrinogenemia has been detected in up to 76% of patients with cirrhosis.[34] Recent studies suggest that these changes to the fibrinogen molecule cause decreased permeability of the formed clot compared to controls and may even confer hypercoagulable features.[35]

Low fibrinogen has been increasingly recognized as an independent risk factor for increased bleeding in patients with cirrhosis. In a study of patients with cirrhosis who were admitted to the ICU, fibrinogen and platelets were significantly reduced compared to other ICU patients. The rate of major bleeding events was increased in patients with cirrhosis and a fibrinogen level below 60 mg/dL.[32] In a nationwide United Kingdom study of blood use in cirrhotic patients admitted to the hospital, fibrinogen was found to be an independent predictor of mortality, with a 29% increase in mortality for every 1 g/L (100 mg/dL) reduction in fibrinogen.[36] Low fibrinogen levels have been associated with increased risk of bleeding following prophylactic endoscopic variceal band ligation.[37] Studies in orthotopic liver transplantation also suggest using fibrinogen levels as a predictor for excessive intraoperative transfusion.[38]

Maintaining fibrinogen levels above 100-120 mg/dL have been proposed by several societies and expert groups in the setting of acute blood loss.[39,40] Replacement of fibrinogen with cryoprecipitate is generally preferred over fresh frozen plasma due to the large infusion volume associated with the latter. These recommendations, however, have not been adequately studied in a clinical trial and it remains unclear what constitutes an adequate fibrinogen level. Moreover, fibrinogen threshold levels and transfusion recommendations have not been tailored for patients with cirrhosis and dysfibrinogenemia. Further studies are warranted to investigate an appropriate fibrinogen target for patients with cirrhosis and the utility of cryoprecipitate for acute blood loss and procedural prophylaxis.

6 | HEMOSTATIC AGENTS

6.1 | Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) was originally developed and approved for the treatment of bleeding episodes in patients with hemophilia A complicated by anti-factor VIII allo-antibodies. rFVII is thought to act at sites of vascular injury through thrombin generation and formation of fibrin (Figure 1).[41] The rationale behind trialing rFVIIa in liver disease is that although the coagulopathy is thought to be "balanced", the balance is unstable and could easily be tipped in the direction of bleeding or thrombosis or the other by minor triggers.[5,42] The most recent randomized, double-blind studies of cirrhotic patients with upper gastrointestinal bleeding and variceal bleeding have not shown overall effect of rFVIIa on arrest of bleeding, reduction of rebleeding or short-term mortality.[43,44] Interestingly, however, in the patients with variceal bleeding, those that received rFVIIa compared to placebo had a significantly lower 42-day mortality. As such, the most recent consensus guidelines on the use of rFVIIa as an adjunctive treatment for massive bleeding conclude that rFVIIa is not recommended for patients in Child-Pugh A cirrhosis (grade B evidence); however, use in patients with more advanced liver disease is uncertain (grade C evidence).[45]

rVFIIa has also been studied as a prophylactic agent prior to orthotopic liver transplantation.[46,47] Although initially promising, more recent randomized controlled trials have found no benefit in terms of perioperative transfusion requirements with rVFIIa.[48] Similarly, the results of two systematic reviews and meta-analyses[49,50] as well as a Cochrane review[51] have found no differences in mortality or transfusion requirements between patients receiving rFVIIa or placebo prior to liver transplantation. Lastly, enthusiasm for rVFIIa has waned since it is introduction in 2005 as prothrombin complex concentrates (PCC) with factor VII became available.

6.2 | Prothrombin complex concentrates (PCC)

Prothrombin complex concentrates (PCC) are hemostatically active concentrates that contain factors II, IX and X and variable amounts of factor VII with a final overall clotting factor concentration approximately 25 times higher than normal plasma (Figure 1).[52] PCC were found to be non-inferior compared to FFP in cases of urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists in patients with acute major bleeding.[53] Additional factors that make PCC attractive over FFP are the speed with which PCC can be administered, owing to the fact that it does not require blood-type matching or thawing, and the relatively small infusion volume. 2012 Chest guidelines on anticoagulant therapy recommend PCC over FFP for rapid reversal of anticoagulation in vitamin K antagonist (VKA)-associated major bleeding.[54]

The role of PCC is not well defined in patients with cirrhosis-related coagulopathy and major bleeding. While evidence and guidelines are scarce on this topic, the National Advisory Committee (NAC) on Blood and Blood Products of Canada does not recommend PCC for coagulopathy associated with liver dysfunction.[55] A multi-center, randomized controlled trial is currently underway to address whether PCC vs placebo prior to surgery will reduce transfusion requirements in cirrhotic patients undergoing liver transplantation.[56] The remainder of literature on PCC in cirrhotic patients is limited to retrospective studies and case reports, with studies on its use in acute hemorrhagic events being even more rare. The literature

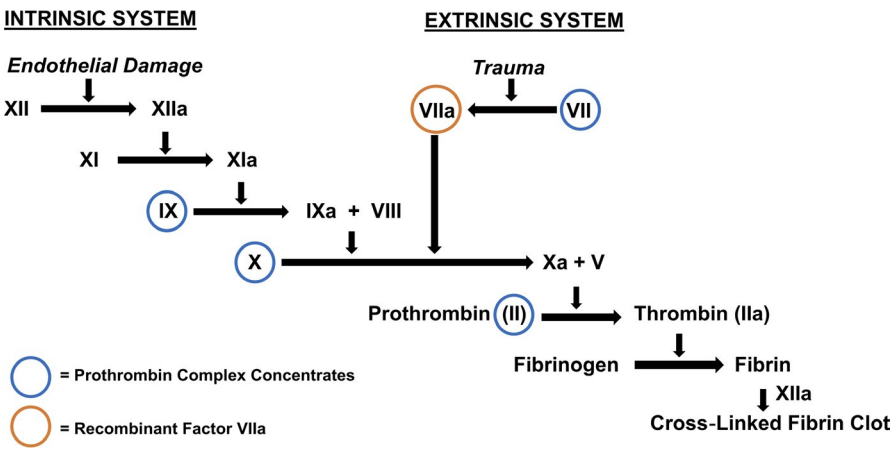

FIGURE 1 Factors provided by prothrombin complex concentrates and recombinant factor VIIa within the coagulation cascade

suggests that PCC effectively reduce INR in patients with cirrhosis but it is still unclear whether this correlates with a reduction in bleeding.[57,58] Kwon et al retrospectively studied patients with cirrhosis who had received PCC, FFP, and rVFIIa prophylactically for a procedure. They found that those who had received PCC had significantly less pRBC and platelet transfusions and lower rates of volume overload compared to FFP.[59] In regards to adverse events, PCC have been associated with increased risk of thromboembolism[60] and DIC[61] and it is unclear at this time whether patients with cirrhosis are at higher risk due to their pro-coagulopathic state. The exact role and safety of PCC in patients with cirrhosis is still unknown.

6.3 | Tranexamic acid

In addition to the decrease in production of anticoagulation and procoagulation factors, hyperfibrinolysis has been found to complicate the coagulopathy of liver disease. Goodpasture initially observed spontaneous fibrinolysis in cirrhotic patients in 1914[62] and since then the existence of hyperfibrinolysis in patients with advanced liver disease has been further supported by analysis of fibrin degradation products and D-dimer.[63] It is under debate whether hyperfibrinolysis is directly related to gastrointestinal bleeding in patients with cirrhosis as all the studies attempting to address this issue are limited by their retrospective nature and small sample size.[34,64,65]

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that inhibits the conversion of plasminogen to plasmin by blocking binding of plasminogen with fibrin. It has been shown to reduce blood transfusions in patients undergoing emergency or urgent surgery,[66,67] decrease postpartum blood loss and prevent postpartum hemorrhage and blood transfusions.[68] Based on a 2015 Cochrane meta-analysis in patients with acute UGIB, TXA appeared to have a beneficial effect on mortality; however, some trials had high dropout rates, limiting the validity of these findings.[69] They recommended additional prospective, randomized, double-blinded studies in order to determine the effects of TXA in the setting of acute UGIB. Several randomized controlled trials are underway to determine whether TXA effectively reduces bleeding, rebleeding, or mortality in UGIB in all-comers[70] and patients with cirrhosis.[71]

In regards to orthotopic liver transplantation, randomized controlled trials have demonstrated efficacy of prophylactic TXA in reducing blood loss and transfusion requirements by approximately 30%-40% compared to placebo.[72,73] A systematic review and meta-analysis of the RCTs did not find a major difference in respect to venous thromboembolic complications, hepatic artery thrombosis, or perioperative mortality; however, the studies were underpowered.[74] A 2011 Cochrane systematic review found no significant difference in 60-day mortality, primary graft non-function, re-transplantation, or thromboembolic episodes between TXA and placebo.[51] However, the authors concluded that all trials were at high risk of bias. Heterogeneity is also a limiting factor given that transplant techniques and outcomes have evolved between the times of the trials. Based on the existing data, prophylactic TXA appears to be beneficial in reducing blood loss and decreasing transfusion requirements during OLT; however, further studies are needed to better define adverse events, optimal dosing, and patient selection. Epsilon Aminocaproic acid (EACA) is an alternative antifibrinolytic agent that was first used in OLT in the 1960s but has not been as extensively studied in this population as TXA. In 2000, a RCT compared prophylactic administration of TXA, EACA, and placebo prior to OLT. EACA reduced transfusion requirements but not statistically significantly compared to placebo, whereas TXA did significantly reduce fibrinolysis and intraoperative transfusion rates.[73] Lastly, aprotinin, another antifibrinolytic agent, that had shown promise in reducing transfusion requirements in OLT,[75] was withdrawn in several countries due to its association with higher mortality rates.[76]

7 | TRANSFUSION GUIDED BY VISCOELASTIC TESTING

Viscoelastic testing (VET) is a technique that evaluates hemostasis using whole blood, taking into account the platelet function, thrombus formation, clot tensile strength, and fibrinolysis. There are three main forms of VET: thromboelasography (TEG), rotational thromboelasometry (ROTEM), and sonorheometry. TEG and ROTEM are the most widely used and share similar principles: In TEG, whole blood is rotated in a cup with a suspended pin (Figure 2) and in ROTEM, whole blood is held in a stationary cup with a central, rotating pin. Sonorheometry, on the other hand, utilizes ultrasound pulses but currently lacks published data for use in liver disease.[77] Viscoelastic testing is a point-of-care, rapid functional assay that is more accurate in predicting the risk in bleeding of a cirrhotic patient than INR or prothrombin time.[25,78]

Figure 2 shows a sample tracing of the TEG assay including common parameters used to quantify results. The R-time refers to the time until clot reaches 2 mm in diameter (s) and corresponds to time to first fibrin formation. The K time refers to time until clot reaches 20 mm in diameter (s) and corresponds to platelet function and fibrin cross-linking. The maximum amplitude (MA) refers to the maximum clot diameter (mm) and corresponds to the summation of platelet, fibrinogen, and factor function. The alpha angle refers to the tangent to the graph when the clot is 2 mm thick (D) and corresponds to the rate of fibrin clot formation. LY30 refers to the clot diameter after 30 minutes and corresponds to fibrinolysis.[77]

VET has been useful in liver transplantation and is widely used at liver transplant centers to guide transfusions of fresh frozen plasma, platelets, and cryoprecipitate during the extensive surgery where coagulation can be severe and dynamic. VET-guided transfusions decrease blood product transfusions during liver transplants compared to transfusions based on standard of care.[79,80] Studies have also shown that VET checked right before liver transplant with MA <47 mm has a sensitivity 90% and specificity 72% to predict if a patient will require massive transfusions of >10 pRBC in the following 24 hours.[81]

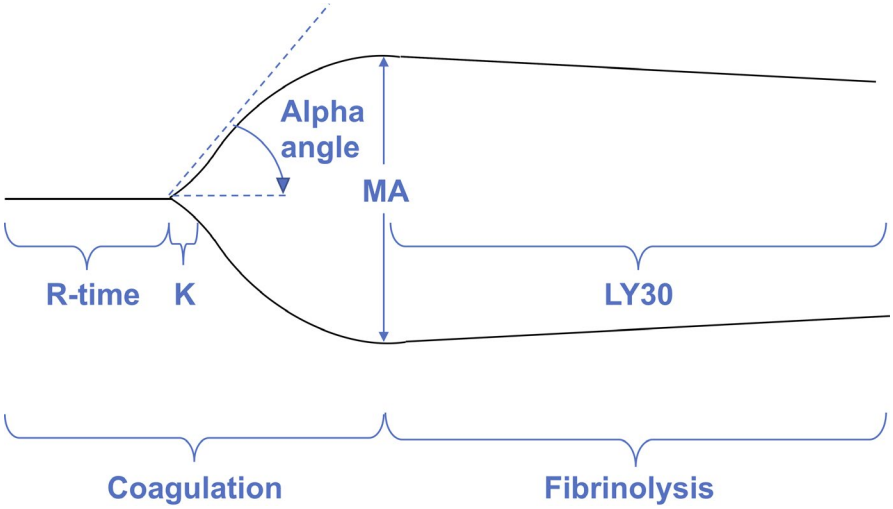

FIGURE 2 Sample thromboelastography (TEG) tracing

Expanding from the use of VET in just liver transplant surgery, VET-guided transfusions can also reduce the number of blood product transfusions before more minor procedures such as central line insertion, paracentesis, TIPS, variceal banding, thoracentesis, liver biopsy, or ERCP as compared to a standard of care guided transfusion rate.[82] The VET group received blood products when the R-time was prolonged outside the laboratory's normal range (12-26 minutes) at >40 minutes or the MA was lower than the laboratory's normal range (42-63 mm) at <30 mm. For the standard of care group, patients received FFP for and INR >1.8 or platelets when the value was $<50 \times 10^9$/L. With a reduced number of blood products in VET-guided transfusions, there were also a reduced number of blood transfusion reactions. Overall bleeding rates were extremely low in low-risk bleeding procedures in both groups.

Recently, a randomized control trial of cirrhotics with acute variceal bleeding was given blood products based on VET-guided transfusions, 13.3% vs. standard of care guided, 100%. The rebleeding rate was similar at 5 days after the acute bleed, but significantly less at 42 days postbleed and 6-week mortality was lower in the VET-guided transfusion group.[83] These findings may be from lower portal pressures from less blood product transfusions which favors having a more restrictive transfusion guideline in cirrhotic patients. Presently, limitations to using the VET-guided transfusion strategies include no standard or guideline for providing transfusions based on VET values and lack of validated risk parameters in the available studies.

8 | BALANCED-RATIO OF PLASMA, PLATELETS, AND PACK RED BLOOD CELLS

Many practice patterns in the management of hemorrhagic shock have been guided by research in trauma literature. In the mid-2000s, the "damage control resuscitation" strategy was proposed to avoid coagulopathy and limit the iatrogenic side effects of resuscitation in hemorrhagic shock.[84] This strategy included rapid source control, early use of a balanced ratio of plasma, platelets and pRBC (in order to mimic whole blood concentrations), limiting excessive crystalloid, and preventing hypothermia and electrolyte disturbances. It has now become common practice to transfuse trauma patients with a blood product ratio of 1:1:1 or 1:1:2 of plasma:platelet:pRBC. More recently, a randomized clinical trial (The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial) studied blood product ratios 1:1:1 vs. 1:1:2 in trauma patients and found that although there was no different in mortality, more patients in the 1:1:1 group achieved hemostasis and fewer died of exsanguination within 24 hours.[85]

Data supporting a fixed ratio, or at the very least a higher FFP and platelet to pRBC ratio are emerging in the OLT literature. In one single-center retrospective study of OLT recipients who required intraoperative pRBC transfusion, those who received FFP:platelet:pRBC in a >1:1:2 ratio vs <1:1:2 ratio had lower pRBC and intraoperative blood product requirements, improved 1-month mortality and 1-year survival.[86] Their data suggest that balanced transfusion may be more important in patients who require massive transfusions (greater than 7-10 units of pRBC), as is consistent with data from the PROPPR trial.[85]

A balanced ratio of plasma, platelet, and pRBC has yet to be studied as a resuscitation strategy in cirrhotic patients with hemorrhagic shock. Given the propensity of patients with cirrhosis to massive GI bleeding, the balanced-ratio transfusion strategy could be a reasonable approach when greater than 7-10 units of pRBC are required. Additional investigation is warranted to evaluate the utility of this approach in this population and study the potential adverse outcomes. A recent study of patients admitted to the ICU with GIB (including patients with cirrhosis) found a significant increase in the risk of transfusion-associated lung injury (TRALI) with use of 1:1:1 transfusion protol.[87] Other potential complications of balanced transfusion include inflammatory-mediated conditions: multiple organ failure, venous thromboembolism, infection,[88,89] and volume-related adverse events such as higher portal venous pressure and increasing risk of rebleeding.[11,12]

9 | WHOLE BLOOD TRANSFUSION

Near the end of World War I and throughout World War II, whole blood transfusions were the standard treatment for military traumatic hemorrhage.[90] Since the advent of blood component therapy, the use of whole blood has fallen out of favor. Blood component therapy allowed for more targeted approach to resuscitation and reduced waste due to longer storage times.[91] Despite these benefits, however, blood component therapy has its share of downsides when it comes to severe hemorrhagic shock. Even a 1:1:1 ratio of blood products yields in a dilute blood mixture with approximately 29% hematocrit, platelet count of roughly 90 x 10^9/L, and coagulation factors only 60% of whole blood concentrations.[92]

Recently, there has been renewed interest in whole blood. The arguments for using whole blood is many-fold: It provides a balanced resuscitation of all blood components that is closest to physiologic blood (including fibrinogen and anticoagulants) and it contains a smaller volume of anticoagulant/preservative solution than individual blood components.[93] In 2014, the Committee on Tactical Combat Casualty Care recommended fresh whole blood (FWB) as the preferred resuscitation product for hemorrhagic shock.[94] Today, 19 leading trauma centers in the United States are using low titer O positive whole blood (LTOWB) for civilian trauma.[95] Seheult et al recently performed a retrospective, observational study of LTOWB use in civilian trauma patients.[96] They found that those who had received LTOWB plus component parts did as well, or better compared to their counterparts who only received component parts.

In a randomized prospective study of 33 patients undergoing OLT, whole blood, when compared to component therapy, was associated with fewer donor exposures and was equally effective in replacement therapy for blood loss.[97] Whether using whole blood over blood component therapy is beneficial in cirrhotic patients with hemorrhagic shock is a question worth exploring and thus far is a question worthy of further study. The lower transfusion volumes as well as the ability to provide blood components that mimic physiologic conditions are two main advantages that whole blood could offer to patients with cirrhosis.

10 | CONCLUSION

In summary, there are multiple possible strategies to provide transfusion support to patients with chronic liver disease, although evidence for many of them is scarce. The strongest evidence is for hemoglobin threshold transfusion with pRBC with the current major guidelines recommending transfusions to a goal of 7-8 g/dL.[2,9] It is common practice to transfuse to a platelet threshold of 50 × 10^9/L in the event of a bleed or invasive procedure based on evidence from in vitro and retrospective studies.[15] Preprocedural administration of TPO receptor agonists has shown promise in increasing platelet levels and reducing platelet transfusions.[21,22] In regards to other threshold-based transfusion strategies, the INR as a marker for coagulopathy has fallen out of favor in cirrhotic patients.[25] There is currently no evidence for an INR threshold prior to any procedures in patients with cirrhosis, and the AASLD currently does not recommend use of FFP as part of the management of portal hypertensive bleed or for prophylactic use prior to paracentesis in response to an elevated INR.[29] Fibrinogen levels have been increasingly recognized as an independent risk factor for increased bleeding and mortality in patients with cirrhosis. Maintaining a fibrinogen level above 100-120 mg/dL has been proposed by several societies in the setting of acute blood loss;[39,40] however, these recommendations have not been specifically tailored or studied for patients with cirrhosis and dysfibrinogenemia.

A number of hemostatic agents have been examined for use in patients with cirrhosis. Thus far, the literature on recombinant activated factor VIIa (rFVIIa) in patients with cirrhosis, either in the setting of UGIB or transplantation, has not shown significant benefit. Current consensus guidelines on the use of rFVIIa as an adjunctive treatment for massive bleeding do not recommend it in patients with Child-Pugh A cirrhosis; however, use in patients with more advanced liver disease is uncertain.[45] The exact role and safety of prothrombin complex concentrates (PCC) and TXA in patients with cirrhosis is still not well defined.[98]

Evidence is expanding for viscoelastic testing (VET). Currently, VET is widely used at liver transplant centers to guide transfusion and has been shown to decrease blood transfusions intraoperatively compared to transfusions based on standard of care.[79] There is an increasing body of evidence that suggests VET-guided transfusions reduce the number of blood products provided in acute variceal bleeding and before minor procedures.[82,83]

In regards to future direction, many groups are still hoping to answer the question of which transfusion strategy is optimal in patients with cirrhosis. The POCKET trial[99] attempted to compare three transfusion strategies (routine coagulation test-guided, ordinary or restrictive, or VET-guided) prior to central venous catheterization in critically ill patients with cirrhosis; however, the trial was terminated early due to low inclusion. The EXARHOSE study (NCT 003023189), currently in the recruitment phase, is a randomized trial of tranexamic acid vs placebo in cirrhotic patients with acute UGIB.[71]

A balanced ratio of transfused blood products has been promising in the setting of hemorrhagic shock due to trauma but has not been specifically studied in patients with cirrhosis. It would be interesting to see if there is a benefit to this transfusion strategy, particularly when greater than 7-10 units of pRBC's are required. Likewise, with the renewed interest in whole blood, it would be worth exploring whether the theoretical ability to provide blood components that mimic physiologic conditions translates to favorable results.

In conclusion, current evidence is limited so providers are left to choose the transfusion strategy based on limited data or extrapolating from non-cirrhotic populations. Future research will hopefully provide safer strategies that will allow for the best patient outcomes while balancing the best resource use.

CONFLICT OF INTEREST

None.

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