14 Physiology, Prevention, and Treatment of Blood Loss During Liver Transplantation

Freeha Arshad, Ton Lisman, and Robert J. Porte

Introduction

Historically, bleeding was one of the major challenges during liver transplantation. The first patient receiving a liver transplant in 1963 exsanguinated during the procedure [1], and massive perioperative blood loss remained a major clinical challenge until the 1980s. Most, if not all, liver transplant procedures required transfusion of blood products in those days, and transfusion requirements could exceed 100 units of red blood cell concentrates (RBCs), whereas mean transfusion requirements were around 20–40 units of blood products (RBC, fresh frozen plasma, platelet concentrates, cryoprecipitate) [2, 3]. Blood products were, and still are, costly and accounted for a significant part of the total costs of liver transplantation [4]. In the last 15–20 years, massive blood loss during liver transplantation has become rare, and a significant proportion of patients can nowadays be transplanted without any requirement for blood transfusion [5]. Improvements in surgical technique and anesthesiological management have contributed to this major reduction in blood loss, but in addition a better understanding of the nature of the abnormalities in the hemostatic system has led to a more rational approach to the prevention of bleeding. Nevertheless, severe and uncontrollable bleeding still occurs occasionally and has to be treated appropriately.

This chapter will discuss causes of bleeding during liver transplantation, strategies to prevent blood loss, and treatment possibilities in case major bleeding does occur.

Hemostatic Alterations in Liver Disease and During Liver Transplantation

The liver is the site of synthesis of most proteins involved in initiation, propagation, and regulation of both coagulation and fibrinolysis. Consequently, major alterations in the levels of hemostatic proteins occur in patients with liver disease (Table 14.1) [6, 7]. In addition, a substantially decreased platelet count is present in a large proportion of patients, which may be accompanied by platelet function defects [8, 9]. Routine diagnostic tests of hemostasis such as platelet count, prothrombin time (PT), and activated partial thromboplastin time (APTT) are consequently frequently abnormal in a patient with liver disease. Abnormal test results have long been interpreted as suggestive of a bleeding tendency [10]. Recent advances in the understanding of both clinical and laboratory aspects of hemostasis in liver disease have led to an alternate view of the status of the hemostatic system in these patients [11]. We have coined this alternate view the "concept of rebalanced hemostasis" in patients

F. Arshad • T. Lisman • R.J. Porte (✉)
Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, University Medical Center Groningen, P.O. Box 30.001, 9700 RB, Groningen, The Netherlands
e-mail: r.j.porte@chir.umcg.nl

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Table 14.1 Alterations in the hemostatic system in patients with liver disease that contribute to bleeding (left) or counteract bleeding (right)

Changes that impair hemostasis	Changes that promote hemostasis
Thrombocytopenia	Elevated levels of von Willebrand factor (VWF)
Platelet function defects	Decreased levels of ADAMTS-13
Enhanced production of nitric oxide and prostacyclin	Elevated levels of factor VIII
Low levels of factors II, V, VII, IX, X, and XI	Decreased levels of protein C, protein S, antithrombin, α_2-macroglobulin, and heparin cofactor II
Vitamin K deficiency	Low levels of plasminogen
Dysfibrinogenemia	
Low levels of α_2-antiplasmin, factor XIII, and TAFI	
Elevated tPA levels	

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with liver disease. The rebalanced hemostasis theory states that with liver disease, the hemostatic system is in a rebalanced status due to concomitant alterations in both pro- and anticoagulant pathways (Fig. 14.1). This balance is present in patients who may have severe abnormalities in routine hemostasis tests such as the PT (either expressed as seconds or as international normalized ration [INR]), APTT, and platelet count indicating that these tests do not reflect the true hemostatic status of patients with complex alterations of hemostasis, for example, seen with liver disease [10]. Patients with liver disease thus do not necessarily have a hemostasis-related bleeding tendency to a degree that is suggested by the low platelet count and/or prolonged PT. Many bleeding complications that occur are unrelated to deranged hemostasis, but rather related to complications of portal hypertension, such as esophageal varices [12, 13]. However, in patients with liver disease, the hemostatic balance is more easily disturbed as compared to healthy individuals, which may lead to bleeding but also to thrombotic complications (summarized in Table 14.1) [11, 14, 15]. Importantly, current laboratory tests, including many newly developed point-of-care tests, fail to predict which patients are at risk for either bleeding or thrombosis.

A thorough review of the pathophysiology of coagulation in liver disease and during liver transplantation is found elsewhere (Chapter 13) in this book.

During liver transplantation additional changes in the hemostatic system occur. During the anhepatic phase there is a lack of synthesis of hemostatic proteins, but more importantly, these proteins (activated hemostatic proteins and protein-inhibitor complexes) accumulate in the circulation due to a lack of clearance by the liver. As a result, disseminated intravascular coagulation can develop, resulting in consumption of platelets and coagulation factors and accompanied by secondary hyperfibrinolysis. During reperfusion, hyperfibrinolysis may further develop as a consequence of release of tissue-type plasminogen activator (tPA) from the graft [16–18]. The degree of hyperfibrinolysis is related to the severity of ischemia/reperfusion injury of the hepatic endothelium, the source of tPA upon graft reperfusion [16, 19]. Moreover, the liver graft may release heparin-like substances which can inhibit coagulation [20]. In addition, hypothermia, metabolic acidosis, and hemodilution may adversely affect the hemostatic status during liver transplantation [5]. Although the additional changes in the hemostatic system during liver transplantation have long been held directly responsible for the bleeding seen in these patients, accumulating evidence suggests that many liver transplant recipients may remain in hemostatic balance throughout the procedure [10, 21, 22]. The hemostatic balance is clinically evident by an increasing proportion of patients that can be transplanted without any blood transfusion [5, 23–26]. Moreover, recent laboratory data indicate rebalanced platelet-mediated hemostasis as a result of a hyperreactive von Willebrand factor system, which is responsible for attachment of platelets to damaged vasculature [27, 28]. Despite profoundly prolonged routine laboratory tests of coagulation (PT, APTT), the coagulation potential appears preserved or even hyperreactive throughout the transplant procedure when tested with modern thrombin generation tests [21]. Finally, with improvements in

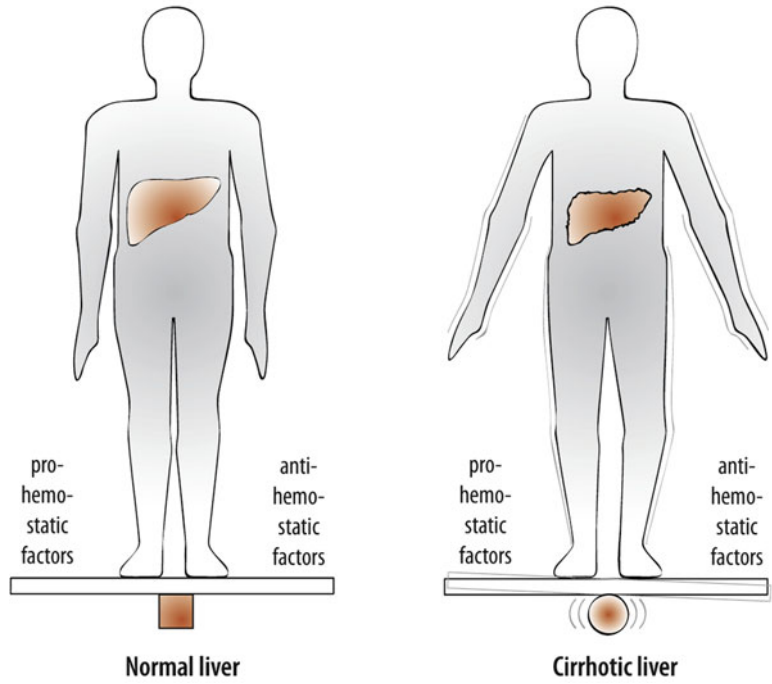

Fig. 14.1 The concept of rebalanced hemostasis in patients with liver disease. In healthy individuals (left), hemostasis is in a solid balance. In patients with liver disease (right), concomitant changes in pro- and antihemostatic pathways result in a "rebalance" in the hemostatic system. This new balance, however, presumably is less stable than the balance in healthy volunteers and may thus more easily tip towards either bleeding or thrombosis

graft preservation and the avoidance of prolonged cold ischemia times, hyperfibrinolysis is nowadays less frequently encountered.

Despite the observation that the hemostatic balance is frequently relatively well preserved during liver transplantation, there are individual patients with severe and uncontrollable bleeding that require substantial amounts of blood products. Causes of these bleeding complications and treatment possibilities will be discussed in this chapter. In addition, there is increasing recognition of the potential for perioperative thrombotic complications. A discussion on diagnosis and treatment of thromboembolic complications during and after liver transplantation is discussed elsewhere (Chapter 13) in this book.

Causes of Bleeding During Liver Transplantation

Liver transplantation is a lengthy procedure with extensive surgical wound surfaces including transsection of collateral veins. Bleeding complications that may occur during the procedure are often due to surgical causes, and meticulous surgical hemostasis is important to limit blood loss. In addition, the presence of portal hypertension may contribute to bleeding and as will be discussed below. Avoidance of aggravation of portal hypertension by fluid restriction and maintenance of a low central venous pressure (CVP) may be required to reduce pressure-associated bleeding complications [23]. There is evidence that a liberal fluid management (including the liberal use of blood products such as fresh frozen plasma) may aggravate the bleeding tendency of patients during liver surgery by increasing CVP and splanchnic venous pressure [5, 23, 29–32]. Strategies to avoid this will be discussed below. Dysfunctional hemostasis may contribute to bleeding in some patients, and multiple potential causes may be present. Firstly, hypothermia, metabolic acidosis, and low ionized calcium levels directly affect the hemostatic system, and prevention and treatment of these complications is important to prevent bleeding [5]. Secondly,

although the role of thrombocytopenia and coagulation factor defects in bleeding during liver transplantation has never been convincingly shown, it has been established that hyperfibrinolysis is associated with an increased bleeding risk [16, 33, 34].

Earlier studies have suggested that patients with a more severe disease are at an increased bleeding risk; however, more recent studies have failed to provide proof for a correlation between disease severity and blood loss [35]. Even more, it has been demonstrated that over time a progressive decrease in transfusion requirements is observed despite a progressive increase in MELD score of the recipients [26]. The most important predictor of blood product use may be the center, or the surgical or anesthesiology team, which may indicate that surgical and anesthesiological factors rather than a defective hemostatic system are the primary cause for perioperative bleeding [36, 37].

Prophylactic Strategies to Prevent Blood Loss

Multiple reasons to support an active attitude towards prevention of bleeding during liver transplantation exist. Firstly, a dry surgical field is beneficial for the surgeon, and lack of bleeding complications will shorten the procedure. Second, excessive blood loss is associated with a worse outcome for multiple reasons, one being the direct detrimental effects of blood product transfusion [38–41]. Finally, reduction of transfusion requirements as well as reduction of the duration of surgery will save costs. Multiple prophylactic strategies to reduce or avoid bleeding exist, and the pros and cons of these strategies will be discussed in the following paragraphs.

Blood Products

In the early days of liver transplantation, prophylactic administration of blood products prior to the procedure was the standard of care. It was believed that (partial) correction of abnormal hemostasis tests prior to surgery would improve the overall hemostatic status of the patients, resulting in a reduced bleeding risk. Consequently, liver transplant procedures routinely started with administration of fresh frozen plasma (FFP) to correct the prolonged PT/APTT, platelet concentrates to reverse thrombocytopenia, and cryoprecipitate to increase the circulating level of fibrinogen [5]. Also, administration of RBCs to reverse anemia is believed to improve hemostasis by virtue of the pivotal role of red blood cells in platelet attachment to the damaged vasculature in flowing blood [42]. During the procedure, frequent monitoring of the hemostatic status by PT, APTT, platelet count, and fibrinogen measurements is performed to guide additional administration of blood products. Alternatively, thromboelastography may be used to guide transfusion [43–45].

Although prophylactic administration of blood products prior to and during liver transplantation is still common practice in many centers, little evidence for the efficacy of such a strategy exists, and there may be valid arguments against prophylactic administration of blood products [5, 12, 32, 46]. Administration of blood products is associated with the potential for volume overload and inevitably results in elevation of CVP and splanchnic venous pressure. This is particularly true in critically ill transplant recipients with a hyperdynamic circulation with increased cardiac output and active shunts between the systemic and portal venous circulation. In a patient with portal hypertension, elevation of CVP by administration of blood products may thus paradoxically induce bleeding by pressure effects rather than decreasing bleeding risk by improving the hemostatic status [30, 31]. Furthermore, administration of blood products is associated with adverse effects and affects morbidity and mortality [23, 24, 47–50], and normalization of routine laboratory tests is hardly ever achieved [51].

Rather than prophylactic administration of blood products in a patient that is not (yet) bleeding, a wait-and-see policy is increasingly used. In this scenario, the anesthesiologist and surgeon accept (profoundly) abnormal PT, APTT, platelet,

and fibrinogen levels, as they do not accurately reflect the hemostatic status and commence with the procedure only to initiate blood product transfusion in case of active bleeding complications [5, 32, 52]. Since abnormal preoperative hemostasis tests do not appear to predict perioperative bleeding risk and many centers can nowadays transplant a large number of patients without any blood transfusions, this wait-and-see policy appears justified [5, 23–26]. When active bleeding does occur, administration of blood products may be guided by laboratory tests or thromboelastography [43, 44]. Specifically, a profound thrombocytopenia in a bleeding patient may be reason for platelet transfusion, whereas a prolonged PT or INR may be reason to transfuse FFP. Furthermore, hypofibrinogenemia may prompt transfusion of fibrinogen concentrate or cryoprecipitate, whereas evidence of hyperfibrinolysis on the thromboelastograph may be a reason to start antifibrinolytic therapy. There is no clear evidence that laboratory-test-based transfusion is optimal in the context of liver transplantation. And, for example, whole blood transfusion is by some as an alternative. No consensus on on-demand transfusion strategies exists, and variability between centers is high [36, 40]. The ratio of blood products administered in bleeding patients is likely important, and some authors have even suggested that whole blood transfusion may be more appropriate than transfusion of individual blood components [53].

Pharmacological Agents

A major advance in management of bleeding complications in liver transplantation has been the use of antifibrinolytic agents. The serine protease inhibitor aprotinin has been shown to reduce transfusion requirements during liver transplantation by around 30–50 % [33, 34, 54], and these findings also indicate that the hyperfibrinolytic status that can accompany liver transplantation is clinically relevant. Aprotinin not only inhibits the fibrinolytic protease plasmin but also has anti-inflammatory properties by virtue of inhibition of kallikrein and the protease-activated receptor type 1 [55]. Administration of aprotinin in liver transplant patients does not appear to be associated with side effects such as thrombosis or renal failure [56–58], which have been reported to occur in cardiac surgery. Despite the apparent excellent risk/benefit profile of aprotinin in liver transplantation, safety concerns in cardiac surgery have led to the withdrawal of aprotinin from the market both in the USA and Europe. The lysine analogues tranexamic acid and ε-aminocaproic acid are potentially suitable alternatives for aprotinin [5]. Although both drugs are widely used, only tranexamic acid has been shown to reduce transfusion requirements in randomized studies [59–61]. It has to be noted that both tranexamic acid and ε-aminocaproic acid are potent antifibrinolytic agents but lack the anti-inflammatory properties of aprotinin.

Other procoagulant drugs may also be beneficial in reducing bleeding. An initial non-controlled trial suggested recombinant factor VIIa (rFVIIa) to reduce transfusion requirements during liver transplantation [62, 63]. However, two subsequent randomized controlled trials did not show any benefit from rFVIIa administration, despite a profound correction of the PT [64, 65]. These findings illustrate that normalization of the PT does not translate in a reduction of bleeding risk, which is in line with the findings that the PT does not predict bleeding risk, and with the laboratory finding that the PT does not accurately reflect the hemostatic status in a patient with liver disease. Although prophylactic administration of rFVIIa does not reduce perioperative blood loss, rFVIIa may be an option as "rescue agent" in patients with intractable bleeding.

Improvement of platelet function parameters, in particular shortening of the bleeding time by administration of 1-deamino-8-D-arginine vasopressin (DDAVP), has not been shown to translate into clinical improvement of hemostasis. Several studies showed no effect of DDAVP on variceal bleeding or on blood loss in patients undergoing partial hepatectomy or liver transplantation [66], indicating that correction of the bleeding time may not necessarily result in improvement of hemostasis.

A pharmacological prohemostatic strategy that may have potential but have not yet been

tested in adequately powered clinical studies is the use of prothrombin complex concentrates (PCCs) to improve the coagulation status. The theoretical advantage of PCCs over FFP is the low volume of PCCs, which prevents the inevitable rise in CVP and splanchnic venous pressure that is accompanied by FFP infusion. On the other hand, PCCs only contain a selection of coagulation factors and its use may be associated with a thrombotic risk. Future randomized clinical trials (RCTs) will have to demonstrate safety and efficacy of PCCs in reducing bleeding during liver transplantation.

Fluid Restriction

Emerging evidence indicates that the hemostatic balance during liver transplantation is relatively well maintained [10] and that portal hypertension, fluid overload, and hyperdynamic circulation are more important determinants of perioperative bleeding than possible coagulation defects [23, 67, 68]. Liver disease and portal hypertension are associated with increased plasma volume and disturbed cardiac function, and the administration of fluids results in a further increase in portal and CVP, promoting rather than preventing bleeding tendencies when surgical damage is inflicted [12, 29–32, 46, 67]. Avoidance of fluid overload by a very conservative transfusion policy and by restriction of infusion of colloids and/or saline thus likely reduces bleeding risk. A recent RCT compared a policy of restrictive transfusions and low CVP with a liberal transfusion policy and found that the former policy leads to a significant reduction in intraoperative blood loss and transfusion requirement, especially during the preanhepatic phase [69]. Liberal use of blood products, including preoperative correction of abnormal laboratory test values may thus even be counterproductive, as these blood products increase venous pressure and thereby "fuel the fire." Some groups have taken more drastic steps to maintain a low perioperative CVP by combining fluid restriction protocols with preoperative phlebotomy [23, 68, 70]. One center has reported that ~80 % of patients could be transplanted without the requirement for any transfusion when using fluid restriction in combination with preoperative phlebotomy [68]. It is important to realize that acceptance of a low hematocrit (20–25 %) is essential in such a strategy. A major concern regarding the use of fluid restriction protocols is the risk of complications such as air embolism, systemic tissue hypoperfusion, and renal failure [24, 68, 71, 72]. Although one non-controlled study showed an increase in renal failure using a low CVP strategy [72], a number of other studies, including one RCT, have concluded that fluid restriction during liver transplantation is safe and does not lead to an increased incidence of postoperative renal failure [23, 68, 69].

Surgical and Anesthesiological Techniques

In general, the experience of the surgical team is an important determinant of perioperative bleeding, but specific improvements in surgical technique have also been instrumental in reducing blood loss [5, 32]. The introduction of the use of venovenous bypass in the 1980s has presumably contributed to a reduction of blood loss, as this technique results in avoidance of major hemodynamic changes during the anhepatic phase [73]. Subsequent introduction of the piggyback technique has led to a significant further decline in transfusion requirements [74, 75]. A major advantage of the piggyback technique with respect to blood loss is the avoidance of dissection of the retroperitoneum, which avoids dissection of multiple collateral veins in this area. More importantly, the piggyback technique has enabled reduction of intraoperative fluid load [74, 75].

Anesthesiological interventions to prevent excessive bleeding are maintenance of body temperature, pH, and ionized calcium level. For example, avoidance of hypothermia is accomplished by heating blankets and administration of fluids at 30° C [5, 72]. Frequent determination of serum-ionized calcium levels and aggressive replacement is key especially when large amount of RBCs are transfused. Citrate that acts as an anticoagulant in RBC by chelating calcium is

metabolized by the liver. With liver disease and especially during the anhepatic phase, plasma citrate levels may be high. Frequent calcium replacement is often required to maintain adequate ionized calcium levels.

Laboratory Monitoring of Bleeding and Transfusion

Traditionally, laboratory tests such as the PT, APTT, platelet count, fibrinogen level, and hematocrit were used to guide transfusion. Cutoffs for transfusion differ substantially from center to center, and it is becoming evident that there is little evidence to support blood product transfusion at certain laboratory thresholds (e.g., a platelet count below 50×10^9/L or a PT > 1.5–2 times the upper limit of normal) in the absence of active bleeding [32, 33, 40, 46]. Even in the presence of active bleeding, target laboratory values to be achieved have never been thoroughly established. However, aiming for a hemostatic profile of platelet count $>50 \times 10^9$/L, PT < 1.5–2 times the upper limit of normal, and a fibrinogen level of 1–2 g/L appears reasonable. Instead of using these classic laboratory values, the use of thromboelastography has been suggested to result in a more rational use of blood product transfusion although definitive data are lacking. The thromboelastography tracing can distinguish between a specific platelet or coagulation defect and is the only available rapid test that can indicate hyperfibrinolysis. Thromboelastography tracing can thus guide platelet, FFP, fibrinogen transfusion, and possibly antifibrinolytic therapy [43, 45]. Some centers use thromboelastography for prophylactic transfusion of blood products, whereas other centers only transfuse blood products in case of active bleeding. There are an increasing number of variations of the thromboelastograph on the market which differ in coagulation trigger (none, tissue factor, kaolin) or in additive that specifically neutralize specific components of coagulation (heparins, platelets, fibrinolysis). The true value of native or variant thromboelastography in guiding transfusion or predicting bleeding remains to be established.

Adverse Events of Blood Products

A large intracenter variability in blood product use during liver transplantation exists [36]. Part of this variability may be explained by differences in the surgical experience of the teams, but an important contributor to this variability is the lack of uniformity of transfusion protocols. An important difference between centers is the choice between prophylactic administration of blood products based on pre- and perioperative laboratory parameters and an on-demand approach in which blood products are only transfused when active bleeding occurs. When deciding to transfuse blood products, one has to weigh the possible (and in liver transplantation often uncertain) benefits against potential adverse events.

A number of adverse effects associated with blood product use are well recognized [48, 76]. Although the risk of viral transmission has not yet been fully eliminated, the chance of contracting a virus through blood product transfusion is extremely low, at least in the western world [39, 77]. Transmission of bacteria can still occur, in particular with transfusion of platelet concentrates which are stored at room temperature, which increases the risk of bacterial growth [49, 78, 79]. Hemolytic and allergic transfusion reactions have been well described but are fortunately relatively rare [76]. A recently recognized risk of blood product transfusion is transfusion-related acute lung injury (TRALI), an antibody-mediated transfusion reaction that is rare, but may be fatal [80]. The risk of TRALI appears highest with the use of FFP, in particular FFP from female donors [81–83]. Blood product administration results in depression of the immune response, which in theory may be beneficial with liver transplantation as it may contribute to prevention of rejection. However, transfusion-related immune modulation also increases the incidence of postoperative infections. Finally, fluid overload is an important potential complication of transfusion of blood products [50].

The introduction of transfusion-free liver transplantation has allowed us the assessment of the effects of blood product transfusion. Several

studies have demonstrated that blood product transfusion is associated with increased morbidity and mortality even after thorough adjustment for potential confounders [38, 84, 85]. Adverse events of transfusion are still observed at low doses of blood products. Furthermore, a dose effect has been demonstrated, indicating that in patients who received some blood products during the transplantation, further minimization of transfusion may be of the utmost importance [5].

Conclusion: A Rational Approach to Prevention or Treatment of Bleeding

Increasing laboratory evidence suggests that the hemostatic system in a patient with liver disease is in a rebalanced situation and consequently much more competent than suggested by routine laboratory tests such as the PT and platelet count. During liver transplantation, the hemostatic status appears to remain in balance, when tested by more sophisticated laboratory tests. These findings, combined with the clinical observations that an increasing number of centers report that a substantial number of patients can undergo a liver transplantation without any blood transfusion, suggest that dysfunctional hemostasis is not necessarily the prime cause for perioperative bleeding. Nevertheless, occasionally patients with dysfunctional hemostasis as the primary cause for excessive blood loss are encountered, and hyperfibrinolysis is often observed in these patients.

Clinical experience suggests that portal hypertension, fluid overload, and the hyperdynamic circulation are much more important determinants of bleeding than a dysfunctional hemostatic system. Volume contraction therefore may be vital in avoiding bleeding during transplantation. Volume contraction is achieved by restrictive use of fluids and blood products, avoidance of fluid overload, and a very restrictive use of blood products. Preoperatively, correction of a prolonged PT or decreased platelet count is not required and may even be counterproductive as transfusion of these products can result in elevation of the CVP and splanchnic venous pressure. Perioperatively, transfusion of blood products should be restricted to situations in which active bleeding not of surgical origin occurs. Transfusion may be guided by laboratory values or thromboelastography, although little evidence for the efficacy of this strategy exists. The restrictive use of blood products may also be of benefit for long-term outcome, since multiple studies suggest that transfusion in liver transplant recipients is associated with increased morbidity and mortality. Antifibrinolytics may be used to reduce fibrinolytic bleeding, either prophylactically or on-demand, except in patients with a high thrombotic risk, such as patients with cholestatic disease who demonstrate hypercoagulability on the thromboelastograph. Finally, the acceptance of low hematocrit values (20–25 %) as part of a restrictive transfusion policy appears to be safe.

Although transfusion thresholds and protocols have not been established, it appears reasonable that, in case of larger transfusion requirements, RBC, FFP, and platelets should be concomitantly administered in physiological ratios. On-demand use of antifibrinolytics may be considered, especially with evidence of hyperfibrinolysis on thromboelastography. Also, the use of rFVIIa may be considered, but little data on efficacy and safety are available. This drug is also extraordinarily expensive. Additional studies on the optimal management of intractable bleeding during liver transplantation are required; however, it will be difficult to achieve adequate power for these studies.

References

1. Starzl TE, Marchioro TL, Von Kaulla KN, Hermaan G, Brittain RS, Waddell WR. Homotransplantation of the Liver in Humans. Surg Gynecol Obstet. 1963; 117:659–76.
2. Lewis JH, Bontempo FA, Cornell F, et al. Blood use in liver transplantation. Transfusion. 1987;27(3):222–5.
3. Farrar RP, Hanto DW, Flye MW, Chaplin H. Blood component use in orthotopic liver transplantation. Transfusion. 1988;28(5):474–8.
4. Showstack J, Katz PP, Lake JR, et al. Resource utilization in liver transplantation: effects of patient characteristics and clinical practice. NIDDK Liver Transplantation Database Group. JAMA. 1999; 281(15):1381–6.

5. de Boer MT, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. Dig Surg. 2005;22(4):265–75.
6. van der Werf J, Porte RJ, Lisman T. Hemostasis in patients with liver disease. Acta Gastroenterol Belg. 2009;72(4):433–40.
7. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. J Hepatol. 2002;37(2):280–7.
8. Hugenholtz GG, Porte RJ, Lisman T. The platelet and platelet function testing in liver disease. Clin Liver Dis. 2009;13(1):11–20.
9. Lisman T, Porte RJ. The role of platelets in liver inflammation and regeneration. Semin Thromb Hemost. 2010;36(2):170–4.
10. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood. 2010;116(6):878–85.
11. Lisman T, Caldwell SH, Burroughs AK, et al. Hemostasis and thrombosis in patients with liver disease: the ups and downs. J Hepatol. 2010;53(2):362–71.
12. Westerkamp AC, Lisman T, Porte RJ. How to minimize blood loss during liver surgery in patients with cirrhosis. HPB (Oxford). 2009;11(6):453–8.
13. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362(9):823–32.
14. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case–control study. Am J Gastroenterol. 2009;104(1):96–101.
15. Senzolo M, Sartori MT, Lisman T. Should we give thromboprophylaxis to patients with liver cirrhosis and coagulopathy? HPB (Oxford). 2009;11(6):459–64.
16. Porte RJ, Bontempo FA, Knot EA, Lewis JH, Kang YG, Starzl TE. Systemic effects of tissue plasminogen activator-associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. Transplantation. 1989;47(6):978–84.
17. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg. 1985;64(9):888–96.
18. Lewis JH, Bontempo FA, Awad SA, et al. Liver transplantation: intraoperative changes in coagulation factors in 100 first transplants. Hepatology. 1989;9(5):710–4.
19. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. Blood. 1988;71(4):1090–5.
20. Senzolo M, Cholongitas E, Thalheimer U, et al. Heparin-like effect in liver disease and liver transplantation. Clin Liver Dis. 2009;13(1):43–53.
21. Lisman T, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. J Hepatol. 2010;52(3):355–61.
22. Warnaar N, Lisman T, Porte RJ. The two tales of coagulation in liver transplantation. Curr Opin Organ Transplant. 2008;13(3):298–303.
23. Massicotte L, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. Liver Transpl. 2006;12(1):117–23.
24. Cacciarelli TV, Keeffe EB, Moore DH, et al. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. Arch Surg. 1999;134(1):25–9.
25. Ramos HC, Todo S, Kang Y, Felekouras E, Doyle HR, Starzl TE. Liver transplantation without the use of blood products. Arch Surg. 1994;129(5):528–32. discussion 532–3.
26. Jabbour N, Gagandeep S, Shah H, et al. Impact of a transfusion-free program on non-Jehovah's Witness patients undergoing liver transplantation. Arch Surg. 2006;141(9):913–7.
27. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology. 2006;44(1):53–61.
28. Pereboom IT, Adelmeijer J, van Leeuwen Y, Hendriks HG, Porte RJ, Lisman T. Development of a severe von Willebrand factor/ADAMTS13 disbalance during orthotopic liver transplantation. Am J Transplant. 2009;9(5):1189–96.
29. Jarnagin WR, Gonen M, Maithel SK, et al. A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. Ann Surg. 2008;248(3):360–9.
30. Smyrniotis V, Kostopanagiotou G, Theodoraki K, Tsantoulas D, Contis JC. The role of central venous pressure and type of vascular control in blood loss during major liver resections. Am J Surg. 2004;187(3):398–402.
31. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. Br J Surg. 1998;85(8):1058–60.
32. Alkozai EM, Lisman T, Porte RJ. Bleeding in liver surgery: prevention and treatment. Clin Liver Dis. 2009;13(1):145–54.
33. Porte RJ, Molenaar IQ, Begliomini B, et al. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. Lancet. 2000;355(9212):1303–9.
34. Findlay JY, Rettke SR, Ereth MH, Plevak DJ, Krom RA, Kufner RP. Aprotinin reduces red blood cell transfusion in orthotopic liver transplantation: a prospective, randomized, double-blind study. Liver Transpl. 2001;7(9):802–7.
35. Massicotte L, Beaulieu D, Roy JD, et al. MELD score and blood product requirements during liver transplantation: no link. Transplantation. 2009;87(11):1689–94.
36. Ozier Y, Pessione F, Samain E, Courtois F. French Study Group on Blood Transfusion in Liver

Transplantation. Institutional variability in transfusion practice for liver transplantation. Anesth Analg. 2003;97(3):671–9.
37. Massicotte L, Sassine MP, Lenis S, Roy A. Transfusion predictors in liver transplant. Anesth Analg. 2004;98(5):1245–51. table of contents.
38. de Boer MT, Christensen MC, Asmussen M, et al. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. Anesth Analg. 2008;106(1):32–44. table of contents.
39. Dodd RY. Current risk for transfusion transmitted infections. Curr Opin Hematol. 2007;14(6):671–6.
40. Lopez-Plaza I. Transfusion guidelines and liver transplantation: time for consensus. Liver Transpl. 2007;13(12):1630–2.
41. Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. Semin Cardiothorac Vasc Anesth. 2004;8(4):267–81.
42. Lisman T, Caldwell SH, Porte RJ. Anemia as a potential contributor to bleeding in patients with liver disease—neglected but not forgotten. J Hepatol. 2011;54(3):594–5.
43. Wang SC, Shieh JF, Chang KY, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc. 2010;42(7):2590–3.
44. Tripodi A, Primignani M, Chantarangkul V, et al. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. Thromb Res. 2009;124(1):132–6.
45. Salooja N, Perry DJ. Thromboelastography. Blood Coagul Fibrinolysis. 2001;12(5):327–37.
46. Steib A, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. Can J Anaesth. 2001;48(11):1075–9.
47. Brems JJ, Hiatt JR, Colonna 2nd JO, et al. Variables influencing the outcome following orthotopic liver transplantation. Arch Surg. 1987;122(10):1109–11.
48. Benson AB, Burton Jr JR, Austin GL, et al. Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following liver transplantation. Liver Transpl. 2011;17(2):149–58.
49. Juffermans NP, Prins DJ, Vlaar AP, Nieuwland R, Binnekade JM. Transfusion-related risk of secondary bacterial infections in sepsis patients: a retrospective cohort study. Shock. 2011;35(4):355–9.
50. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion. 2011;51(2):338–43.
51. Youssef WI, Salazar F, Dasarathy S, Beddow T, Mullen KD. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. Am J Gastroenterol. 2003;98(6):1391–4.
52. Massicotte L, Beaulieu D, Thibeault L, et al. Coagulation defects do not predict blood product requirements during liver transplantation. Transplantation. 2008;85(7):956–62.
53. Laine E, Steadman R, Calhoun L, et al. Comparison of RBCs and FFP with whole blood during liver transplant surgery. Transfusion. 2003;43(3):322–7.
54. Pereboom IT, de Boer MT, Porte RJ, Molenaar IQ. Aprotinin and nafamostat mesilate in liver surgery: effect on blood loss. Dig Surg. 2007;24(4):282–7.
55. Poullis M, Manning R, Laffan M, Haskard DO, Taylor KM, Landis RC. The antithrombotic effect of aprotinin: actions mediated via the protease activated receptor 1. J Thorac Cardiovasc Surg. 2000;120(2):370–8.
56. Molenaar IQ, Porte RJ. Aprotinin and thromboembolism in liver transplantation: is there really a causal effect? Anesth Analg. 2002;94(5):1367–8. author reply 1368.
57. Molenaar IQ, Legnani C, Groenland TH, et al. Aprotinin in orthotopic liver transplantation: evidence for a prohemostatic, but not a prothrombotic, effect. Liver Transpl. 2001;7(10):896–903.
58. Molenaar IQ, Begliomini B, Grazi GL, et al. The effect of aprotinin on renal function in orthotopic liver transplantation. Transplantation. 2001;71(2):247–52.
59. Dalmau A, Sabate A, Acosta F, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. Anesth Analg. 2000;91(1):29–34.
60. Boylan JF, Klinck JR, Sandler AN, et al. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. Anesthesiology. 1996;85(5):1043–8. discussion 30A-31A.
61. Kaspar M, Ramsay MA, Nguyen AT, Cogswell M, Hurst G, Ramsay KJ. Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. Anesth Analg. 1997;85(2):281–5.
62. Hendriks HG, Meijer K, de Wolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. Transplantation. 2001;71(3):402–5.
63. Hendriks HG, Meijer K, de Wolf JT, et al. Effects of recombinant activated factor VII on coagulation measured by thromboelastography in liver transplantation. Blood Coagul Fibrinolysis. 2002;13(4):309–13.
64. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. Liver Transpl. 2005;11(8):973–9.
65. Planinsic RM, van der Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. Liver Transpl. 2005;11(8):895–900.
66. Wong AY, Irwin MG, Hui TW, Fung SK, Fan ST, Ma ES. Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy. Can J Anaesth. 2003;50(1):14–20.
67. Balci ST, Pirat A, Torgay A, Cinar O, Sevmis S, Arslan G. Effect of restrictive fluid management and acute normovolemic intraoperative hemodilution on transfusion requirements during living donor hepatectomy. Transplant Proc. 2008;40(1):224–7.

68. Massicotte L, Perrault MA, Denault AY, et al. Effects of phlebotomy and phenylephrine infusion on portal venous pressure and systemic hemodynamics during liver transplantation. Transplantation. 2010;89(8):920–7.
69. Feng ZY, Xu X, Zhu SM, Bein B, Zheng SS. Effects of low central venous pressure during preanhepatic phase on blood loss and liver and renal function in liver transplantation. World J Surg. 2010;34(8):1864–73.
70. Hashimoto T, Kokudo N, Orii R, et al. Intraoperative blood salvage during liver resection: a randomized controlled trial. Ann Surg. 2007;245(5):686–91.
71. Melendez JA, Arslan V, Fischer ME, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg. 1998;187(6):620–5.
72. Schroeder RA, Collins BH, Tuttle-Newhall E, et al. Intraoperative fluid management during orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 2004;18(4):438–41.
73. Shaw Jr BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg. 1984;200(4):524–34.
74. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg. 1989;210(5):649–52.
75. Jovine E, Mazziotti A, Grazi GL, et al. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. Transpl Int. 1997;10(2):109–12.
76. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood. 2008;112(7):2617–26.
77. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. Curr Opin Hematol. 2003;10(6):412–8.
78. Stroncek DF, Rebulla P. Platelet transfusions. Lancet. 2007;370(9585):427–38.
79. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008;358(12):1229–39.
80. Lee JS, Gladwin MT. Bad blood: the risks of red cell storage. Nat Med. 2010;16(4):381–2.
81. Eder AF, Herron Jr RM, Strupp A, et al. Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006–2008). Transfusion. 2010;50(8):1732–42.
82. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion. 1985;25(6):573–7.
83. Densmore TL, Goodnough LT, Ali S, Dynis M, Chaplin H. Prevalence of HLA sensitization in female apheresis donors. Transfusion. 1999;39(1):103–6.
84. Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. Anesth Analg. 2009;108(4):1083–91.
85. Hendriks HG, van der Meer J, de Wolf JT, et al. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. Transpl Int. 2005;17(11):673–9.