Fibrinogen Supplementation and Its Indications

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Abstract

Adequate plasma levels of fibrinogen are essential for clot formation, and in severe bleeding, fibrinogen reaches a critically low plasma concentration earlier than other coagulation factors. Although the critical minimum concentration of fibrinogen to maintain hemostasis is a matter of debate, many patients with coagulopathic bleeding require fibrinogen supplementation. Among the treatment options for fibrinogen supplementation, fibrinogen concentrate may be viewed by some as preferable to fresh frozen plasma or cryoprecipitate. The authors review major studies that have assessed fibrinogen treatment in trauma, cardiac surgery, end-stage liver disease, postpartum hemorrhage, and pediatric patients. Some but not all randomized controlled trials have shown that fibrinogen concentrate can be beneficial in these settings. The use of fibrinogen as part of coagulation factor concentrate based therapy guided by point-of-care viscoelastic coagulation monitoring (ROTEM [rotational thromboelastometry] or TEG [thromboelastography]) appears promising. In addition to reducing patients' exposure to allogeneic blood products, this strategy may reduce the risk of complications such as transfusion-associated circulatory overload, transfusion-related acute lung injury, and thromboembolic adverse events. Randomized controlled trials are challenging to perform in patients with critical bleeding, and more evidence is needed in this setting. However, current scientific rationale and clinical data support fibrinogen repletion in patients with ongoing bleeding and confirmed fibrinogen deficiency.

Keywords
- coagulopathy
- fibrinogen
- hemorrhage
- perioperative

The causes of coagulopathic surgical bleeding are complex and multifactorial. Factors that contribute to coagulopathy include hemodilution, acquired platelet dysfunction, coagulation factor consumption (e.g., in extracorporeal circuits), activation of fibrinolytic, fibrinogenolytic and inflammatory pathways, and hypothermia. In addition, hemostatic defects can be caused by prescribed oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) or platelet inhibitors. Congenital disorders such as von Willebrand's disease and hemophilia represent additional potential causes of bleeding, although these are less common. The management of perioperative bleeding requires identification of the possible causes, accurate diagnosis of the coagulopathy using laboratory or point-of-care testing, and treatment with needed allogeneic blood products and/or coagulation factor concentrates.

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The overall aims of therapy are to restore hemostasis and minimize blood loss while avoiding any unnecessary transfusions. Despite the frequent use of allogeneic blood products, these are associated with major risks that include transfusion-related acute lung injury (TRALI), immunological reactions, and transfusion-transmitted diseases.[1–3] To minimize the likelihood of transfusion-related side effects, there has been a shift in mainland Europe from empirical coagulation therapy with major bleeding (e.g., administration of red blood cells (RBCs), fresh frozen plasma (FFP), and platelets with a fixed 1:1:1 ratio) to early, targeted treatment with recombinant and purified coagulation factor concentrates.[4] The use of such products is supported by their immediate availability, low administration volume, rapid administration, and a high degree of viral safety.

Importance of Fibrinogen

Adequate plasma levels of the coagulation factor fibrinogen are essential to the formation of stable blood clots. Fibrinogen (►**Fig. 1**) is a 340-kDa plasma glycoprotein synthesized in the liver, with a mean half-life of 3 to 5 days.[5] During the process of coagulation, fibrinogen molecules are cleaved by thrombin into fibrin monomers, which then form a fibrin net that enmeshes platelets.

In severe bleeding, fibrinogen reaches critically low plasma concentrations at an earlier stage than other coagulation factors.[6] The normal range for plasma fibrinogen concentration is around 2 to 4.5 g/L, although slight variations on this range are used by different laboratories due to different reagents used for fibrinogen measurement. Higher levels are observed during pregnancy, often > 5 g/L during the third trimester. The critical minimum concentration of fibrinogen to maintain hemostasis is a matter of debate. Guidelines from the American Society of Anesthesiologists Task Force on Perioperative Blood Management recommend fibrinogen supplementation for patients with bleeding and a plasma fibrinogen level below 0.8 to 1 g/L,[7] but more recent European guidelines recommend threshold levels of 1.5 to 2 g/L relating to perioperative bleeding and trauma.[8,9] In practice, the critical threshold for fibrinogen is probably affected by the availability of other hemostatic factors (e.g., thrombin). For the assessment of functional fibrinogen levels in the setting of surgery, viscoelastic coagulation tests may be considered preferable to the Clauss assay because they can be performed rapidly at the point-of-care. For example, in the FIBTEM assay (performed using a rotational thromboelastometry [ROTEM] device), amplitude at 10 minutes following the start of clot formation (A10) allows early identification of fibrinogen deficiency. FIBTEM A10 values below 10 mm have been suggested as a trigger for fibrinogen substitution.[8,10] Viscoelastic studies have shown that clot strength increases linearly with fibrinogen concentration suggesting that irrespective of the baseline plasma level, fibrinogen supplementation will always increase clot strength.[11]

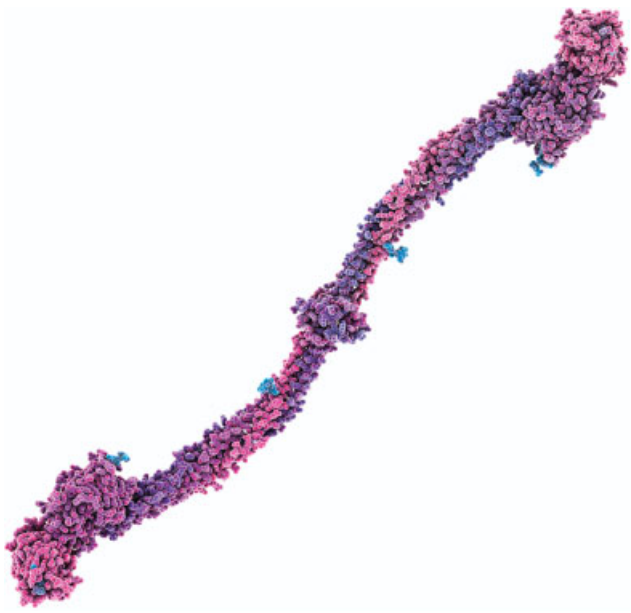

Fig. 1 Fibrinogen molecule. (Reproduced with permission from Laguna Design/Science Photo Library.)

Fibrinogen Supplementation Strategies

There are three possible treatment options for fibrinogen supplementation that include FFP, cryoprecipitate, and fibrinogen concentrate. The main drawback with FFP is that a large volume is often required to achieve a clinically meaningful increase in the patient's plasma fibrinogen level.[12] This is attributed to the concentration of fibrinogen in FFP being close to (i.e., not far above) the desired level in the patient, which means that fibrinogen levels may not be sufficiently increased when FFP is used. In addition, the risks of complications with FFP, such as transfusion-associated circulatory overload (TACO) and TRALI, should be considered. Cryoprecipitate provides a higher concentration of fibrinogen than FFP (typically 10–20 g/L) and also contains factor VIII, fibronectin, von Willebrand factor (VWF), and factor XIII[12,13]; however, the concentration of fibrinogen varies considerably between different samples. Cryoprecipitate is commonly used in the United States and the United Kingdom, but it was withdrawn from many European countries due to safety concerns (as it does not undergo pathogen reduction) once fibrinogen concentrate became available. Pasteurized fibrinogen concentrates are pathogen-reduced, and clinical experience shows that the risk of virus transmission is very low (1 in 31,000 doses).[14] It can be reconstituted quickly and is administered without thawing or crossmatching, which enables a short time to infusion. Although fibrinogen concentrate is more expensive than cryoprecipitate or FFP per gram of fibrinogen, which could limit its use in developing countries, it provides a more consistent dose, 20 g/L, than either cryoprecipitate or FFP. Fibrinogen concentrate is licensed in several countries worldwide for treatment and prophylaxis in patients with either acquired or congenital fibrinogen deficiency.[15]

Numerous studies in animals and human patients have investigated the effects of supplementary fibrinogen as hemostatic therapy. However, only a limited number of randomized controlled trials (RCTs) have been performed due to the inherent difficulties of performing such investigations in patients with major bleeding. Available data on the effects of fibrinogen supplementation are somewhat discordant. This review discusses evidence from clinical

and experimental studies of fibrinogen supplementation in clinical settings where such treatment is most likely to be required.

Trauma

Trauma-induced coagulopathy is an important cause of mortality and can occur early after injury. Coagulopathy may be exacerbated by consumption and dilution of coagulation factors, as well as hypothermia, acidosis, and hyperfibrinolysis. Plasma concentrations of fibrinogen below 1.5 g/L have been documented in 73% of patients with hemoglobin lower than 100 g/L upon hospital admission and 63% of those with base excess lower than –6 mmol/L.[16] Low fibrinogen levels on arrival at the emergency room, or diminished strength of the fibrin-based clot, has been associated with increased transfusion requirements and increased mortality.[17–19] A retrospective military study reported decreased mortality among seriously injured soldiers treated with a high versus low fibrinogen:RBC ratio.[20] These data imply that early fibrinogen supplementation may be beneficial in severely injured bleeding patients. Treatment approaches in trauma-related bleeding, including approaches to restoring low fibrinogen levels (e.g., whether to use FFP, cryoprecipitate, or fibrinogen concentrate; what threshold to use for triggering fibrinogen therapy), differ greatly among trauma centers. Similar to other international guidelines, the European guidelines for managing trauma recommend treatment with fibrinogen in trauma patients with significant bleeding and signs of functional fibrinogen deficit or a plasma fibrinogen level less than 1.5 to 2 g/L.[9]

Allogeneic blood products, particularly FFP, are administered in many centers as the principal means of achieving hemostasis. However, FFP transfusion is associated with risks of later multiple organ failure, acute respiratory distress syndrome, TRALI, and TACO.[21–23] Administration of FFP to bleeding patients may stabilize plasma fibrinogen levels, avoiding further decrease, but provides limited scope to achieve clinically significant increases in fibrinogen levels.[12] In contrast, cryoprecipitate or fibrinogen concentrate enables plasma fibrinogen levels to be raised as needed, and such treatment can be guided by viscoelastic coagulation tests. Retrospective studies have shown that coadministration of fibrinogen along with other coagulation factors (e.g., prothrombin complex concentrate [PCC]), as goal-directed coagulation management defined by a treatment algorithm (►**Fig. 2**), is potentially effective in the management of trauma-related bleeding. In a retrospective review of 128 bleeding trauma patients, this treatment approach was associated with lower mortality than that predicted by the Trauma Injury Severity Score and the Revised Injury Severity Classification score.[24] Another retrospective study by the same investigators showed that requirements for allogeneic blood product transfusion were lower in trauma patients treated with fibrinogen concentrate and/or PCC versus patients treated with FFP.[19] A third retrospective study was conducted by a different group of investigators in 294 trauma patients to evaluate whether administration of fibrinogen concentrate improved patient outcomes.[25] Despite a reduction in mortality after 6 hours, fibrinogen concentrate had no significant impact on overall mortality. A prospective observational study was reported in 223 bleeding patients treated with fibrinogen concentrate, most (92%) of whom also received FFP.[26] Statistically significant positive correlations were observed between plasma fibrinogen levels (both at the end of surgery and 24 hours postoperatively) and survival, suggesting that fibrinogen supplementation may improve the likelihood of survival.

The single-center RETIC study performed by Innerhofer et al is currently the only RCT to have assessed fibrinogen supplementation in trauma-related bleeding.[27] First-line coagulation factor concentrates were compared with FFP in patients who were bleeding or expected to bleed. A treatment algorithm was used, in which the doses of FFP and fibrinogen concentrate were 15 mL/kg bodyweight and 50 mg/kg, respectively. After interim analysis of 100 patients (of whom 48 received FFP and 52 received coagulation factor concentrates), the trial was terminated early due to high risks of treatment failure and massive transfusion in the FFP arm. A significantly higher percentage of patients receiving FFP versus coagulation factor concentrates required rescue therapy (52 vs. 4%; $p < 0.0001$), and the percentages of patients receiving massive transfusion were 30 versus 12% ($p = 0.042$).[27]

Based on current evidence, the extent to which fibrinogen concentrate is beneficial in patients with trauma-related bleeding is still a matter of debate. RCTs are challenging to perform in this field, but more data from such studies are clearly needed.

Cardiopulmonary Bypass and Cardiac Surgery

The conduct of cardiac surgery requiring the use of cardiopulmonary bypass (CPB) can cause major perturbations in coagulation. Patients' coagulation status may be compromised due to several reasons such as hemostatic activation and consumption of coagulation factors during and after CPB, the effects of heparin and protamine, hypothermia, and hemodilution.[28] Furthermore, many patients are on oral anticoagulants that may not be discontinued before surgery, which subsequently increases the risk of bleeding. Given the multifactorial causes of coagulopathy, we recommend the use of point-of-care viscoelastic coagulation monitoring to allow for rapid, targeted therapy.

At the onset of CPB, the patient's blood is diluted due to priming of the bypass circuit with crystalloids and/or colloids.[29,30] Subsequently, nonphysiological flow patterns within the bypass circuit (e.g., shear effects) can affect plasmatic and cellular components of hemostasis.[28] Interactions between the blood and the circuit include activation and binding of coagulation factors and platelets, leading to reductions in plasma levels and/or function of these constituents.[28,31,32] Heparin is administered before CPB to prevent the blood from clotting in the bypass circuit, but hemostatic activation still occurs and can cause depletion of coagulation factors as well as thrombocytopenia and platelet dysfunction.[28] Furthermore, in a single study, it

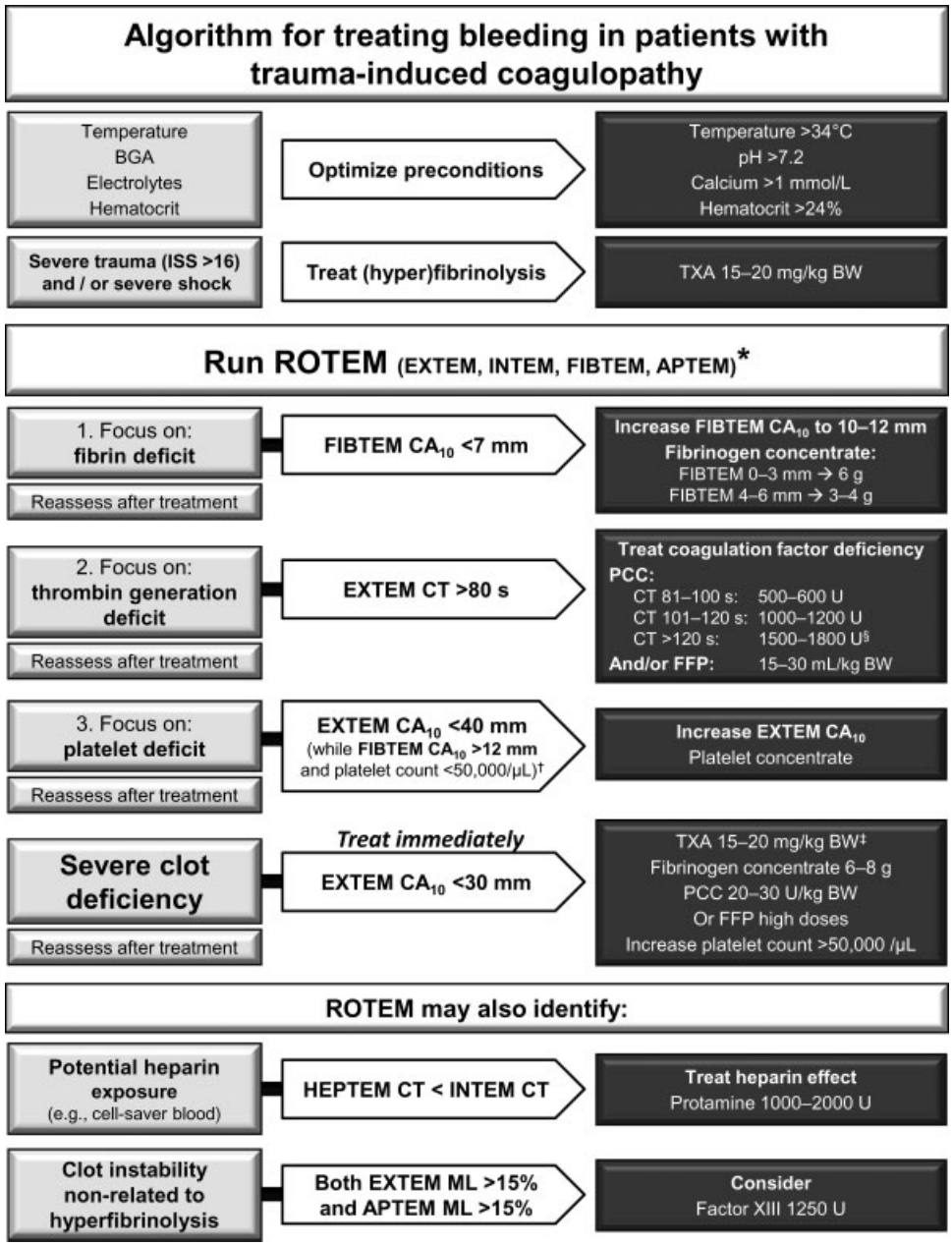

Fig. 2 Algorithm for managing trauma-induced coagulopathy and diffuse microvascular bleeding. *For patients who are unconscious or known to be taking platelet inhibitor medication, Multiplate tests (adenosine diphosphate test, arachidonic acid test, and thrombin receptor activating peptide-6 test) are also performed. §If decreased antithrombin III (ATIII) is suspected or known, consider coadministration of ATIII. †Any major improvement in extrinsically activated test plus aprotinin or tranexamic acid (APTEM) parameters compared with corresponding EXTEM parameters may be interpreted as a sign of hyperfibrinolysis. ‡Only for patients not receiving TXA at an earlier stage of the algorithm. BGA, blood gas analysis; BW, body weight; Ca, calcium; CT, clotting time; FFP, fresh frozen plasma; ISS, injury severity score; ML, maximum lysis; PCC, prothrombin complex concentrate; TXA, tranexamic acid. (Reproduced with permission from Schöchl H, Schlimp C. Trauma bleeding management: the concept of goal-directed primary care. Anesth Analg 2014;119(5):1064–1073.)

was suggested that fibrin formation is impaired during CPB to a greater extent than either thrombin generation or the platelet component of clot strength.[32] This suggests that fibrinogen deficiency may be an important cause of ongoing bleeding in both adult and pediatric cardiac surgery. The risk of major bleeding is substantially increased when fibrinogen levels drop below 1.5 to 2 g/L.[33]

Data on the early use of fibrinogen concentrate in adult cardiac surgery are conflicting. In a single-center, prospective, double-blinded RCT, patients undergoing complex cardiac surgery, with CPB duration predicted to exceed 90 minutes, were randomized to receive fibrinogen concentrate or placebo.[34] The dose of fibrinogen concentrate was designed to achieve a target FIBTEM maximum clot firmness (MCF) of 22 mm, and this resulted in a median dose of 4 g. Patients in the placebo arm received the equivalent volume as saline solution. The percentage of patients avoiding treatment with any allogeneic blood product was 67.2% with fibrinogen concentrate and 44.8% with placebo (odds ratio: 0.40; $p = 0.015$). Moreover, there was a significant reduction in median postoperative blood loss in the

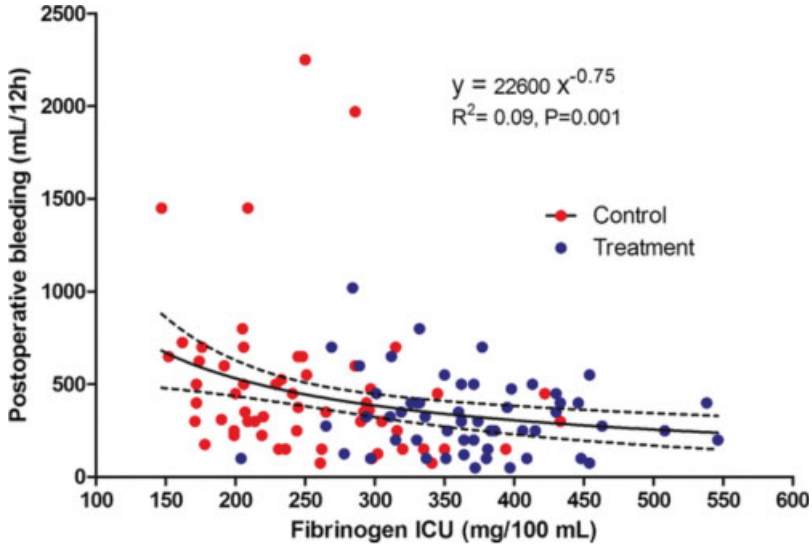

Fig. 3 Association between plasma fibrinogen levels and bleeding in cardiac surgery. The negative relationship remained significant ($p = 0.05$) after adjustment for treatment arm. (Reproduced from Ranucci M, Baryshnikova E, Crapelli GB, et al; Surgical Clinical Outcome REsearch (SCORE) Group. Randomized, Double-Blinded, Placebo-Controlled Trial of Fibrinogen Concentrate Supplementation After Complex Cardiac Surgery. Am J Heart Assoc 2015;4(6):e002066, licensed under CC BY-NC 4.0.)

fibrinogen concentrate arm: 300 versus 355 mL; $p = 0.042$. A significant negative association was found between plasma fibrinogen levels upon arrival at the intensive care unit (ICU) and the amount of postoperative bleeding (►**Fig. 3**). No thromboembolic events occurred in patients who had received fibrinogen concentrate. As this was a single-center study that excluded important groups of patients (e.g., anemic), the generalizability of results is not known.

Another double-blinded placebo-controlled phase 3 RCT (REPLACE) assessed fibrinogen concentrate as first-line treatment for bleeding in complex cardiovascular surgery patients after separation from bypass and surgical hemostasis.[35] As in the aforementioned study, the dose of fibrinogen concentrate was based on a target FIBTEM MCF of 22 mm. The median number of units of allogeneic blood products transfused during 24 hours after administration of study treatment (primary endpoint) was 5 with fibrinogen concentrate and 3 with placebo ($p = 0.026$). Also, 5-minute bleeding mass decreased from pre- to postadministration of fibrinogen concentrate by 20 g and decreased from pre- to postadministration of placebo by 19.5 g ($p = 0.32$). The results of this study were unexpected and may have been related to the low rates of adherence to the study protocol or the criteria for administering study treatment (nonstandard method for measuring bleeding and the lack of significant hypofibrinogenemia seen in adult patients undergoing CPB). A previous randomized phase 2 study performed using similar methods at a single center reported a statistically significant reduction in the median 24-hour transfusion of allogeneic blood products in patients treated with fibrinogen concentrate versus placebo (2 vs. 13 units; $p < 0.001$), but this study also had important limitations.[36] In addition, several cohort studies performed in patients undergoing different types of cardiovascular surgery (aortic valve operation and ascending aorta replacement, thoracoabdominal aortic aneurysm surgery, coronary artery bypass grafting) suggested that FIBTEM-guided fibrinogen concentrate therapy postbypass can reduce requirements for transfusion of allogeneic blood products.[37–39]

Use of fibrinogen concentrate along with other coagulation factors according to a coagulation management algorithm that included point-of-care viscoelastic coagulation testing has been investigated in cardiovascular surgery and has been shown to reduce transfusions of allogeneic blood products.[40] Overall, there is a rationale for fibrinogen supplementation as an essential part of coagulation therapy in cardiac surgery patients with bleeding after separation from CPB. The use of fibrinogen concentrate may reduce patients' requirements for allogeneic blood products, reduce bleeding rates, and improve treatment safety, but confirmatory and more definitive data are required. The effects of fibrinogen repletion using fibrinogen concentrate compared with cryoprecipitate in this setting have been studied further in the multicenter, active-control, single-blinded phase 3 FIBrinogen REplenishment in Surgery (FIBRES) RCT, the results of which are expected shortly.[41]

End-Stage Liver Disease

Patients with end-stage liver disease (ESLD) have an increased risk of bleeding due to multiple hemostatic abnormalities. ESLD is associated with reduced concentrations of both pro- and anticoagulant proteins. On the procoagulant side, a deficiency of vitamin K-dependent coagulation factors (II, VII, IX, X) is typically accompanied by thrombocytopenia. Reduced levels of vitamin K-dependent factors prolong the prothrombin time (PT), and this may be interpreted as an increased bleeding risk. However, anticoagulants such as proteins C and S are also vitamin K-dependent, meaning that their levels are also decreased, and this is not evident from routine coagulation or viscoelastic tests.[42] Patients with ESLD present with chronic inflammation, depending on portal hypertension,[43] which can affect hemostasis. An increase in plasma levels of VWF results at least partly

from a deficiency of the hepatically synthesized protease ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs), serving as compensation for thrombocytopenia. Plasma levels of factor VIII are three times higher in ESLD patients than in healthy volunteers.[44] Cirrhosis has been associated widely with laboratory changes favoring hyperfibrinolysis, such as increased levels of tissue plasminogen activator (t-PA) and reduced levels of thrombin-activatable fibrinolysis inhibitor (TAFI) and α-2 antiplasmin. However, in patients with ESLD, the balance of fibrinolysis seems to be restored by corresponding changes to the antifibrinolytic pathways.[45,46]

Overall, patients with ESLD have rebalanced hemostasis (i.e., physiological procoagulant and anticoagulant factors are both reduced, sometimes to the same extent), implying that when hemorrhage does occur, it should not be assumed based on tests such as PT that there is a need for procoagulant therapy.[47] The main reason for bleeding in this patient population is portal hypertension,[44] and there is more likely to be a risk of thrombosis than bleeding.[48] Coagulation management guided by viscoelastic testing using a ROTEM or thromboelastography (TEG) device together with clinical considerations such as the extent and nature of bleeding is suggested.[49] Blasi et al hypothesized that baseline (presurgery) thromboelastometry data may predict perioperative transfusion requirements.[50] They found that EXTEM A10 < 35 mm before surgery is highly predictive of blood transfusion during surgery. In another study, FIBTEM A10 > 13 mm in liver transplant patients at the time of admission to the ICU was shown to provide a negative predictive value for postoperative bleeding of 95.8%.[51] As an example, this would mean that for 1,000 patients who had FIBTEM > 13 mm, 958 would not bleed.

Plasma levels of fibrinogen in ESLD may be normal or decreased but due to modified oxidation of the fibrin polymer, the fibrin net is less permeable and less sensitive to fibrinolysis.[52] Although in other settings such as trauma, low plasma fibrinogen levels (< 1 g/L) may be associated with a higher risk of spontaneous bleeding, this is not necessarily the case in patients with ESLD. In healthy adults, fibrinogen contributes approximately 16% of clot elasticity; in liver failure, this percentage remains similar (~14%) despite the strength of the fibrin-based clot being reduced by approximately 38%.[53–56] The minimum plasma level of fibrinogen needed to prevent bleeding in ESLD is yet to be established definitively. Based on the results of a prospective study, Nadim et al recommended levels of 1 to 1.5 g/L before surgical procedures are undertaken.[57] Another prospective trial showed that fibrinogen levels < 0.6 g/L were associated with spontaneous bleeding in ESLD, but in this setting, this would also reflect deficiency of other coagulation factors, thrombocytopenia, and enhanced fibrinolysis.[58] In relation to viscoelastic coagulation testing, a FIBTEM MCF of 8 to 10 mm appears sufficient for the prevention of spontaneous bleeding.[51] Therefore, we would advocate fibrinogen supplementation in bleeding ESLD patients with FIBTEM MCF < 8 mm.

ROTEM-guided treatment with coagulation factor concentrates was assessed in a study of liver transplant patients, in which fibrinogen concentrate was administered with a target FIBTEM MCF of 6 mm and PCC was given with a target EXTEM MCF of 35 mm. Transfusion of allogeneic blood products was low, with median values of 2 units of RBCs and no units of FFP and platelets (►**Fig. 4**).[59] Thirty-six percent of transplants were performed without administering any RBCs, FFP transfusion was avoided in 85% of cases, and platelets were not required in 71% of cases. Fifty-eight percent of patients were treated with fibrinogen concentrates and the median dose was 6.3 g. The low rate of blood product use in this study supports the use of fibrinogen concentrates in this setting, with guidance from viscoelastic testing.

The question of whether preemptive fibrinogen supplementation might be beneficial before surgical procedures in ESLD patients was explored by Sabate et al in a prospective randomized trial.[60] The treatment group received preemptive fibrinogen concentrate with a targeted fibrinogen plasma level of 2.9 g/L before undergoing liver transplantation, whereas no preemptive treatment was administered to the control group. Once surgery started, fibrinogen concentrate could be administered in either group if fibrinogen levels fell below 1 g/L. Patients in the treatment group received a median fibrinogen dose of 3.54 g preemptively and a total of 4.14 g over 24 hours, with the latter being significantly

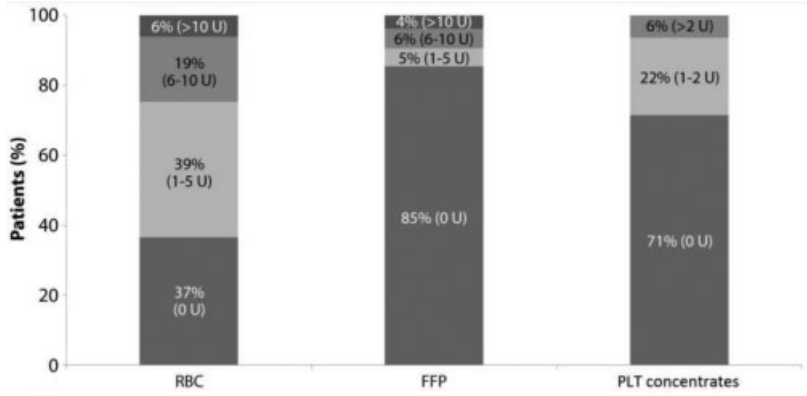

Fig. 4 Transfusion of allogeneic blood products in liver transplant patients receiving ROTEM-guided treatment with coagulation factor concentrates including fibrinogen ($N = 266$). (Reproduced with permission from Kirchner C, Dirkmann D, Treckmann JW, et al. Coagulation management with factor concentrates in liver transplantation: a single-center experience. Transfusion 2014;54(10 Pt 2):2760–2768.)

higher than in the control group (2.58 g). However, transfusion rates for RBCs and platelets were not reduced by preemptive treatment. Based on our observations, we suggest that fibrinogen supplementation should only be administered to liver transplantation patients who are bleeding.

Postpartum Hemorrhage

Globally, postpartum hemorrhage (PPH) is the leading cause of maternal deaths.[61] Pregnancy has a marked influence on the delicate balance that normally exists between procoagulants, the anticoagulant system, and the fibrinolytic process. Levels of fibrinogen, VWF, factors VII, VIII, IX, X, XII, TAFI, and PAI-1 are increased, whereas antagonists of coagulation such as protein C and antithrombin remain largely unchanged and protein S and t-PA decrease.[62] These changes leave the pregnant woman in a theoretical prothrombotic state at the end of the third trimester to help combat the hemorrhagic challenge presented by childbirth.

Fibrinogen depletion in early PPH is predictive of progression to severe PPH, suggesting a causative relationship for ongoing bleeding.[63–66] For the management of PPH, the use of algorithms or massive hemorrhage protocols can help reduce overall transfusion requirements and hemorrhage-associated morbidity. Due to lack of adequate evidence, there is a wide variation in managing PPH. In some hospitals, blood products are administered preemptively with a fixed ratio of RBC, FFP, and platelets, despite the paucity of evidence for this approach.[67] Women in the third trimester of pregnancy generally have a fibrinogen level of 4 to 6 g/L, whereas FFP derived from nonpregnant donors has a fibrinogen level of approximately 2 g/L. Therefore, the administration of FFP as part of a formulaic approach may be counterproductive and cause a reduction of fibrinogen levels. Cryoprecipitate is a more concentrated source of fibrinogen and can therefore be used to increase the patient's plasma fibrinogen level. However, in PPH as in other settings, fibrinogen concentrate may be considered preferable due to easy (rapid) administration, convenient storage, standardized fibrinogen content, and low risk of complications such as transmission of pathogens and TRALI.

When and How Should Fibrinogen Be Supplemented in a Bleeding Parturient?

Prepartum fibrinogen levels do not appear to affect the risk of PPH.[68] Therefore, prophylactic administration of fibrinogen before delivery appears unlikely to be beneficial.

A recent multicenter RCT in PPH compared fibrinogen concentrate with placebo in women with a modest PPH (1,000–1,500 mL blood loss) and a modest drop in fibrinogen levels (FIBTEM A5 < 16 mm).[69] Fibrinogen concentrate administered with the aim of restoring FIBTEM A5 to > 22 mm did not produce statistically significant reductions in transfusion of allogeneic blood products or blood loss. A prespecified subgroup analysis suggested that FIBTEM A5 > 12 mm or fibrinogen > 2 g/L is sufficient for hemostasis. As shown in ►**Fig. 5**, in patients with low pretreatment fibrinogen levels, fibrinogen concentrate therapy was associated with reductions in transfusions and bleeding.

In an observational study, two cohorts of patients with an estimated blood loss of > 1,500 mL and FIBTEM A5 < 12 mm (indicative of plasma fibrinogen level < 2 g/L) were compared.[70] The first cohort was treated with "shock packs" (4 units of RBCs, 4 units of FFP, and 1 unit of platelets), and the second cohort received ROTEM-guided fibrinogen concentrate as first-line intervention, with allogeneic blood products subsequently given as needed. The criteria for administering fibrinogen concentrate (dose: 3 g) were FIBTEM A5 < 7 mm or FIBTEM A5 7 to 12 mm with active bleeding. After each dose, FIBTEM A5 was reassessed, and if the criteria were still met, an additional dose of fibrinogen concentrate was given; this cycle was continued until the criteria were no longer met. The median number of units of allogeneic blood products administered was 8 for patients treated with shock packs and 3.2 for patients treated with fibrinogen concentrate ($p = 0.0004$). The percentages of patients developing TACO in the two treatment groups were 9.5 and 0%, respectively ($p = 0.038$).

The results of an extension of this study, covering 32,647 deliveries, have been accepted for publication.[71] Out of 893 patients with estimated blood loss > 1,500 mL, only 203 (23%) had FIBTEM A5 ≤ 12 mm, of whom 110 met the criteria for fibrinogen concentrate therapy. The total amount of fibrinogen administered ranged from 3 to 18 g, but 67% of patients needed only a single dose of 3 g. Higher doses were most commonly needed by women with placental abruption (which is commonly associated with disseminated intravascular coagulation and excessive consumption of clotting factors) or those with massive blood loss (≥ 3,500 mL). As in the original study, FIBTEM-guided treatment with fibrinogen concentrate was associated with statistically significant reductions in the administration of allogeneic blood products. For example, only 11 of the fibrinogen concentrate-treated patients required FFP, 8 of whom had placental abruptions. Fibrinogen supplementation also reduced the incidence of TACO, decreased the rate of ICU admission, and produced a nonsignificant reduction in the percentage of women requiring hysterectomy over the 4-year study period.

Low or falling plasma fibrinogen levels appear to be associated with severe PPH, and the available evidence suggests a critical threshold of 2 g/L. In most women with moderate bleeding, plasma fibrinogen levels do not fall below this threshold. Therefore, the administration of FFP is likely to reduce the patient's fibrinogen level and aggravate bleeding, increasing the need for RBC transfusions; this may lead to volume overload, which potentially necessitates ICU admission. Patients in whom fibrinogen levels fall below 2 g/L (FIBTEM A5 < 12 mm) may benefit from treatment with fibrinogen concentrate, although well-designed RCTs are needed for confirmation.

Pediatric Patients

Plasma fibrinogen levels in children older than 1 year are comparable to low normal levels in adults. However, infants younger than 1 year have lower levels; this may be attributable to the fact that they have the fetal form of fibrinogen that has a different structure to adult fibrinogen, although the

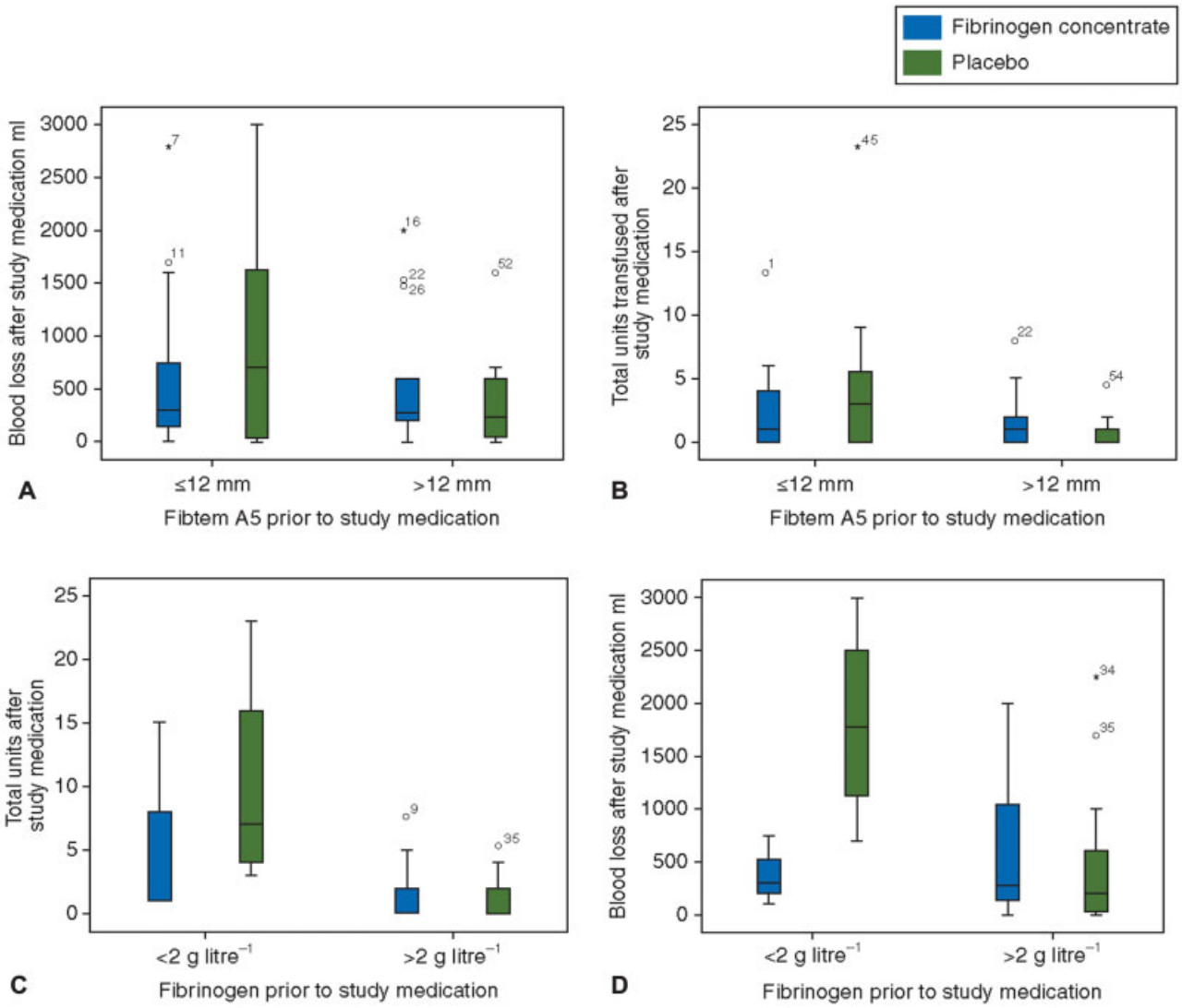

Fig. 5 Fibrinogen concentrate therapy in postpartum hemorrhage: effects on blood loss and transfusion of allogeneic blood products within 24 hours of study treatment in patients with FIBTEM A5 levels ≥ or < 12 mm, and plasma fibrinogen levels above or below 2 g/L. (Reproduced with permission from Collins PW, Cannings-John R, Bruynseels D, et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum hemorrhage: OBS2, a double-blind randomized controlled trial. Br J Anaesth 2017;119(3):411–421.)

functional activity is similar.[72,73] No critical minimum level of fibrinogen in children has been universally accepted, but hypofibrinogenemia plays a key role in the development of acquired perioperative coagulopathy.[74–78] For example, intraoperative fibrinogen levels during major surgery appear to influence the extent of intraoperative and postoperative bleeding as well as transfusion requirements.[79,80] Australian guidelines for blood management in children recommend fibrinogen supplementation when criteria similar to those used in adults are met (fibrinogen level < 1.5 g/L; target level of 2 g/L in cases of critical bleeding).[8,81]

The effects of intraoperative fibrinogen substitution have been investigated in adult studies across a range of clinical settings, but data from pediatric surgical patients are scarce.[79,80,82–84] In a randomized clinical trial performed in children undergoing major craniofacial or spinal surgery, intraoperative fibrinogen concentrate was administered using one of two FIBTEM MCF threshold values as a trigger, < 8 mm (conventional) or < 13 mm (early substitution), to maintain fibrinogen levels throughout surgery.[80] Early substitution led to a significant reduction in blood loss and transfusion of RBCs among children undergoing craniosynostosis surgery, although no significant differences were observed in those undergoing scoliosis surgery (►**Fig. 6**). No intra- or postoperative transfusions of plasma or platelets were necessary in any of the study participants despite considerable blood loss, and no treatment-related adverse events were observed. Economic analysis performed in craniosynostosis patients showed that compared with conventional fibrinogen supplementation, early substitution incurred no significant increase in the total cost of coagulation management (including allogeneic blood products and coagulation factors).[85] Posthoc analysis of study data revealed that a fibrinogen concentrate dose of 50 mg/kg was needed to increase FIBTEM MCF by approximately 5 mm and that higher doses up to 100 mg/kg were needed

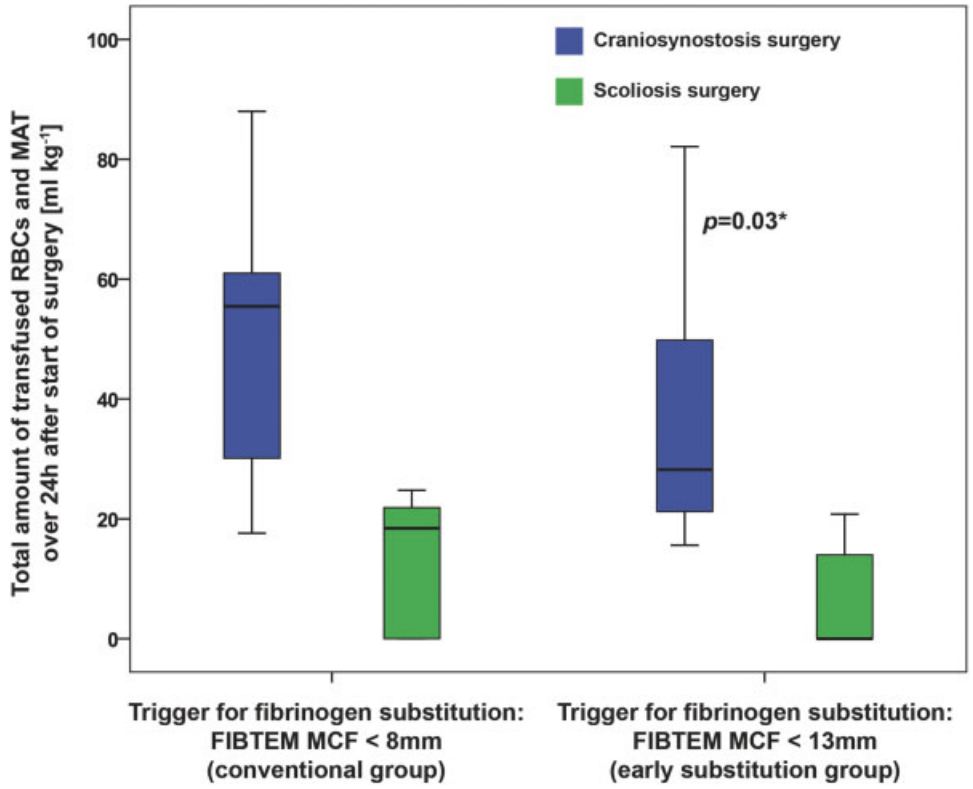

Fig. 6 The effect of early versus conventional supplementation of fibrinogen on 24-hour transfusion of red blood cells (RBCs) and mechanically processed autologous transfusions (administered as a replacement for RBCs) in major pediatric surgery. (Reproduced with permission from Haas T, Spielmann N, Restin T, et al. Higher fibrinogen concentrations for reduction of transfusion requirements during major pediatric surgery: a prospective randomized controlled trial. Br J Anaesth 2015;115(2):234–243.)

to control bleeding in children with low plasma fibrinogen levels (e.g., below 1 g/L).[86] As in adults, the effect of a specific dose on plasma levels is affected by a series of factors such as the patient's circulation volume, baseline fibrinogen concentration, and administration of other therapies (e.g., RBCs).[12]

In another randomized clinical trial including children undergoing cardiac surgery, fibrinogen concentrate (60 mg/kg) was compared with cryoprecipitate (10 mL/kg) in the management of bleeding after CPB weaning.[82] Fibrinogen concentrate was found to be similarly effective as cryoprecipitate, with no significant differences in posttreatment fibrinogen levels or rates of transfusion of allogeneic blood products. Also, no safety-related differences between the two treatments were evident. In a retrospective review of 50 neonates who underwent elective cardiac surgery, administration of fibrinogen concentrate (70 mg/kg) in the rewarming phase of CPB significantly decreased transfusion of cryoprecipitate and FFP.[84] Three comprehensive reviews of bleeding management during pediatric major surgery have been published in recent years.[83,87,88] All of them emphasized the benefits of goal-directed use of coagulation factors such as fibrinogen concentrate, especially when guided by viscoelastic assays. A meta-analysis of 14 randomized clinical trials involving 1,035 adult and pediatric surgical patients demonstrated that fibrinogen concentrate therapy was associated with reduced bleeding and that it might reduce all-cause mortality.[89] However, this meta-analysis did not include specific (separate) consideration of the pediatric data.

Further studies are warranted to elucidate the potential benefits of administering fibrinogen concentrate to children and to provide guidance regarding appropriate thresholds and doses for timely, effective, and safe coagulation management.

Conclusion

Fibrinogen plays an essential role in the process of coagulation, and plasma levels of fibrinogen are depleted in a range of clinical settings including those discussed previously. For patients with coagulopathic bleeding in the perioperative setting, we suggest point-of-care assessment of the fibrin-based clot (using the FIBTEM assay [ROTEM] or the functional fibrinogen assay [TEG]) to confirm the need for fibrinogen supplementation. Fibrinogen concentrate may be considered by some as preferable to either cryoprecipitate or FFP in patients with hypofibrinogenemia, but direct comparisons are lacking. Deficiencies in the evidence base for fibrinogen concentrate are related to methodological challenges in performing RCTs in patients with critical bleeding. For example, fibrinogen supplementation may have limited efficacy in patients without hypofibrinogenemia, and therefore patients should only be treated after appropriate assessment. Although further evidence is required, current scientific rationale and clinical data provide sufficient basis for administering fibrinogen to patients with ongoing bleeding and confirmed fibrinogen deficiency.

Authors' Contributions

O. G. contributed to preparing the outline. All authors contributed to the writing of the article, critically reviewing the manuscript, and approving the final version for publication.

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Conflicts of Interest

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References

1 Chaiwat O, Lang JD, Vavilala MS, et al. Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology 2009;110(02):351–360
2 Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med 2008;36(04):1114–1118
3 Vamvakas EC, Blajchman MA. Blood still kills: six strategies to further reduce allogeneic blood transfusion-related mortality. Transfus Med Rev 2010;24(02):77–124
4 Grottke O. Coagulation management. Curr Opin Crit Care 2012;18 (06):641–646
5 Weisel JW, Litvinov RI. Fibrin formation, structure and properties. Subcell Biochem 2017;82:405–456
6 Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81(02):360–365
7 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology 2015;122(02):241–275
8 Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol 2017;34(06):332–395
9 Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100
10 Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology 2011;115(06):1179–1191
11 Lang T, Johanning K, Metzler H, et al. The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg 2009;108(03):751–758
12 Collins PW, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. Br J Anaesth 2014;113(04):585–595
13 Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. Transfus Med Rev 2009;23(03):177–188
14 Solomon C, Gröner A, Ye J, Pendrak I. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. Thromb Haemost 2015;113(04):759–771
15 Costa-Filho R, Hochleitner G, Wendt M, Teruya A, Spahn DR. Over 50 years of fibrinogen concentrate. Clin Appl Thromb Hemost 2016;22(02):109–114
16 Schlimp CJ, Voelckel W, Inaba K, Maegele M, Ponschab M, Schöchl H. Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission. Crit Care 2013;17(04):R137
17 Meyer AS, Meyer MA, Sørensen AM, et al. Thrombelastography and rotational thromboelastometry early amplitudes in 182 trauma patients with clinical suspicion of severe injury. J Trauma Acute Care Surg 2014;76(03):682–690
18 Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost 2012;10(07): 1342–1351
19 Schöchl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011;15(02):R83
20 Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 2008;64(2, Suppl):S79–S85, discussion S85
21 Levy JH, Grottke O, Fries D, Kozek-Langenecker S. Therapeutic plasma transfusion in bleeding patients: a systematic review. Anesth Analg 2017;124(04):1268–1276
22 Pandey S, Vyas GN. Adverse effects of plasma transfusion. Transfusion 2012;52(Suppl 1):65S–79S
23 Watson GA, Sperry JL, Rosengart MR, et al; Inflammation and Host Response to Injury Investigators. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma 2009;67(02):221–227, discussion 228–230
24 Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010;14(02):R55
25 Wafaisade A, Lefering R, Maegele M, et al; Trauma Registry of DGU. Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. J Trauma Acute Care Surg 2013;74(02): 387–3, discussion 393–395
26 Weiss G, Lison S, Glaser M, et al. Observational study of fibrinogen concentrate in massive hemorrhage: evaluation of a multicenter register. Blood Coagul Fibrinolysis 2011;22(08):727–734
27 Innerhofer P, Fries D, Mittermayr M, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol 2017;4(06):e258–e271
28 Besser MW, Klein AA. The coagulopathy of cardiopulmonary bypass. Crit Rev Clin Lab Sci 2010;47(5-6):197–212
29 Aronson S, Nisbet P, Bunke M. Fluid resuscitation practices in cardiac surgery patients in the USA: a survey of health care providers. Perioper Med (Lond) 2017;6:15

30 Protsyk V, Rasmussen BS, Guarracino F, Erb J, Turton E, Ender J. Fluid management in cardiac surgery: results of a survey in European cardiac anesthesia departments. J Cardiothorac Vasc Anesth 2017;31(05):1624–1629
31 Blome M, Isgro F, Kiessling AH, et al. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost 2005;93(06):1101–1107
32 Solomon C, Rahe-Meyer N, Sørensen B. Fibrin formation is more impaired than thrombin generation and platelets immediately following cardiac surgery. Thromb Res 2011;128(03):277–282
33 Karkouti K, Callum J, Crowther MA, et al. The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery: an observational study. Anesth Analg 2013;117(01):14–22
34 Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A; Surgical Clinical Outcome REsearch (SCORE) Group. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc 2015;4(06):e002066
35 Rahe-Meyer N, Levy JH, Mazer CD, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (RE-PLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth 2016;117(01):41–51
36 Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology 2013;118(01):40–50
37 Rahe-Meyer N, Pichlmaier M, Haverich A, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth 2009;102(06): 785–792
38 Rahe-Meyer N, Solomon C, Winterhalter M, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 2009; 138(03):694–702
39 Solomon C, Schöchl H, Hanke A, et al. Haemostatic therapy in coronary artery bypass graft patients with decreased platelet function: comparison of fibrinogen concentrate with allogeneic blood products. Scand J Clin Lab Invest 2012;72(02):121–128
40 Weber CF, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology 2012;117(03):531–547
41 Karkouti K, Callum J, Rao V, et al. Protocol for a phase III, non-inferiority, randomised comparison of a new fibrinogen concentrate versus cryoprecipitate for treating acquired hypofibrinogenaemia in bleeding cardiac surgical patients: the FIBRES trial. BMJ Open 2018;8 (04):e020741
42 Saner FH, Gieseler RK, Akız H, Canbay A, Görlinger K. Delicate balance of bleeding and thrombosis in end-stage liver disease and liver transplantation. Digestion 2013;88(03):135–144
43 Mehta G, Gustot T, Mookerjee RP, et al. Inflammation and portal hypertension - the undiscovered country. J Hepatol 2014;61(01): 155–163
44 Saner FH, Abeysundara L, Hartmann M, Mallett SV. Rational approach to transfusion in liver transplantation. Minerva Anestesiol 2018;84(03):378–388
45 Colucci M, Binetti BM, Branca MG, et al. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. Hepatology 2003;38(01):230–237
46 Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. Gastroenterology 2001;121(01): 131–139
47 Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116 (06):878–885
48 Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol 2009;104(01):96–101
49 Saner FH, Kirchner C. Monitoring and treatment of coagulation disorders in end-stage liver disease. Visc Med 2016;32(04): 241–248
50 Blasi A, Beltran J, Pereira A, et al. An assessment of thromboelastometry to monitor blood coagulation and guide transfusion support in liver transplantation. Transfusion 2012;52(09): 1989–1998
51 Dötsch TM, Dirkmann D, Bezinover D, et al. Assessment of standard laboratory tests and rotational thromboelastometry for the prediction of postoperative bleeding in liver transplantation. Br J Anaesth 2017;119(03):402–410
52 Hugenholtz GC, Macrae F, Adelmeijer J, et al. Procoagulant changes in fibrin clot structure in patients with cirrhosis are associated with oxidative modifications of fibrinogen. J Thromb Haemost 2016;14(05):1054–1066
53 Agarwal B, Wright G, Gatt A, et al. Evaluation of coagulation abnormalities in acute liver failure. J Hepatol 2012;57(04): 780–786
54 Peng HT, Nascimento B, Beckett A. Thromboelastography and thromboelastometry in assessment of fibrinogen deficiency and prediction for transfusion requirement: a descriptive review. BioMed Res Int 2018;2018:7020539
55 Scarpelini S, Rhind SG, Nascimento B, et al. Normal range values for thromboelastography in healthy adult volunteers. Braz J Med Biol Res 2009;42(12):1210–1217
56 Solomon C, Ranucci M, Hochleitner G, Schöchl H, Schlimp CJ. Assessing the methodology for calculating platelet contribution to clot strength (platelet component) in thromboelastometry and thrombelastography. Anesth Analg 2015;121(04):868–878
57 Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol 2016;64(03):717–735
58 Drolz A, Horvatits T, Roedl K, et al. Coagulation parameters and major bleeding in critically ill patients with cirrhosis. Hepatology 2016;64(02):556–568
59 Kirchner C, Dirkmann D, Treckmann JW, et al. Coagulation management with factor concentrates in liver transplantation: a single-center experience. Transfusion 2014;54(10 Pt 2):2760–2768
60 Sabate A, Gutierrez R, Beltran J, et al. Impact of preemptive fibrinogen concentrate on transfusion requirements in liver transplantation: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Transplant 2016;16(08):2421–2429
61 World Health Organization. WHO Recommendations on Prevention and Treatment of Postpartum Haemorrhage and the WOMAN Trial. Geneva: World Health Organization; 2017
62 Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth 2012;109(06):851–863
63 Charbit B, Mandelbrot L, Samain E, et al; PPH Study Group. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007;5(02): 266–273
64 Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood 2014;124(11): 1727–1736
65 Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth 2012;108(06): 984–989
66 Gayat E, Resche-Rigon M, Morel O, et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Med 2011;37 (11):1816–1825

67 Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. Br J Haematol 2014;164 (02):177–188

68 Peyvandi F, Biguzzi E, Franchi F, et al. Elevated prepartum fibrinogen levels are not associated with a reduced risk of postpartum hemorrhage. J Thromb Haemost 2012;10(07):1451–1453

69 Collins PW, Cannings-John R, Bruynseels D, et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. Br J Anaesth 2017;119(03):411–421

70 Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia 2015; 70(02):166–175

71 McNamara H, Kenyon C, Smith R, Mallaiah S, Barclay P. Four years' experience of a ROTEM®-guided algorithm for treatment of coagulopathy in obstetric haemorrhage. Anaesthesia 2019;74 (08):984–991

72 Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. Am J Pediatr Hematol Oncol 1990;12(01):95–104

73 Ignjatovic V, Ilhan A, Monagle P. Evidence for age-related differences in human fibrinogen. Blood Coagul Fibrinolysis 2011;22(02):110–117

74 Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. Anesth Analg 2012;114(02):261–274

75 Haas T, Mauch J, Weiss M, Schmugge M. Management of dilutional coagulopathy during pediatric major surgery. Transfus Med Hemother 2012;39(02):114–119

76 Fries D. Dilutional coagulopathy: development, diagnostic options and management [in German]. Haemostaseologie 2006; 26(03, Suppl 1):S15–S19

77 Kozek-Langenecker S. Management of massive operative blood loss. Minerva Anestesiol 2007;73(7-8):401–415

78 Innerhofer P, Kienast J. Principles of perioperative coagulopathy. Best Pract Res Clin Anaesthesiol 2010;24(01):1–14

79 Faraoni D, Willems A, Savan V, Demanet H, De Ville A, Van der Linden P. Plasma fibrinogen concentration is correlated with postoperative blood loss in children undergoing cardiac surgery. A retrospective review. Eur J Anaesthesiol 2014;31(06):317–326

80 Haas T, Spielmann N, Restin T, et al. Higher fibrinogen concentrations for reduction of transfusion requirements during major paediatric surgery: a prospective randomised controlled trial. Br J Anaesth 2015;115(02):234–243

81 National Blood Authority. Patient Blood Management Guidelines: Module 6–Neonatal and Paediatrics. Available at: https://www.blood.gov.au/pbm-module-6. Accessed May 8, 2019

82 Galas FR, de Almeida JP, Fukushima JT, et al. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. J Thorac Cardiovasc Surg 2014;148(04):1647–1655

83 Guzzetta NA, Williams GD. Current use of factor concentrates in pediatric cardiac anesthesia. Paediatr Anaesth 2017;27(07): 678–687

84 Tirotta C, Lagueruela R, Madril D, et al. Use of human fibrinogen concentrate in pediatric cardiac surgery. Int J Anesth Anesth 2015;2(04):1–6

85 Haas T, Spielmann N, Restin T, Schmidt AR, Schmugge M, Cushing MM. Economic aspects of intraoperative coagulation management targeting higher fibrinogen concentrations during major craniosynostosis surgery. Paediatr Anaesth 2016;26(01):77–83

86 Faraoni D. Fibrinogen concentrate as first-line therapy in children undergoing cardiac surgery: promising perspectives. J Thorac Cardiovasc Surg 2015;149(05):1466–1467

87 Maw G, Furyk C. Pediatric massive transfusion: a systematic review. Pediatr Emerg Care 2018;34(08):594–598

88 Goobie SM, Haas T. Perioperative bleeding management in pediatric patients. Curr Opin Anaesthesiol 2016;29(03):352–358

89 Fominskiy E, Nepomniashchikh VA, Lomivorotov VV, et al. Efficacy and safety of fibrinogen concentrate in surgical patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2016;30(05):1196–1204